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01 August 2003

Lone Hartung

PATENT- OG VAREMÆRKESTYRELSEN

DK Trifluoro Benzamides 021125

NOVEL BENZAMIDE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS

Field of the invention

The present invention relates to novel compounds that interact with a melanin-concentrating hormone receptor, a MCH receptor. The compounds have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimina etc. or in the treatment or prevention of depression.

The invention also relates to therapeutic and/or prophylactic use of the compounds, to processes for the preparation of the novel compounds, to pharmaceutical compositions comprising the compounds, to the manufacture of such compositions and to methods for the treatment and/or prevention of MCH receptor related disorders.

Background of the invention

Melanin-concentrating hormone (MCH) is a cyclic peptide that originally was isolated from salmoid pituitaries. In the fish, the 17 amino acid peptide causes aggregation of melanin and inhibits the release of ACTH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse and human exhibiting 100% amino acid identity. In the last decades there has been increasing activity in the research in the physiologic roles of MCH. It has been reported that MCH is involved in the feeding or body weight regulation, in energy balance, in response to stress, in water balance, in energy metabolism, in the general arousal/attention state, memory and cognitive functions and in psychiatric disorders. The biological effects of MCH are believed to be mediated by specific MCH receptors, and the MCH1 and MCH2 receptors have been described. Antagonists of MCH receptor (e.g. MCH1 receptor) may be suitable for use as obesity or weight reducing agents and they are also believed to have antidepressant and/or anxiolytic properties.

The present invention provides novel compounds that have a MCH modulating activity, i.e. antagonistic, inverse agonistic/negative antagonism, allosteric modulator, partial agonist or agonistic action.

Detailed description of the invention

The term "alkenyl" is intended to indicate an unsaturated alkyl group having one or more double bonds.

The term "alkynyl" is intended to indicate an unsaturated alkyl group having one or more triple bonds.

The term "cycloalkyl" is intended to denote a cyclic, saturated alkyl group of 3-7 carbon atoms.

The term "cycloalkenyl" is intended to denote a cyclic, unsaturated alkyl group of 5-7 carbon atoms having one or more double bonds.

The term "alkoxy" is intended to indicate the group alkyl-O-.

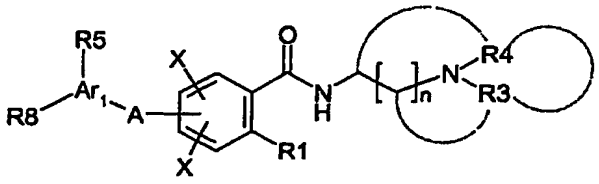
The term "aryl" is intended to denote an aromatic (unsaturated), typically 6-membered, ring, which may be a single ring (e.g. phenyl) or fused with other 5- or 6-membered rings (e.g. naphthyl or indole).

The term "heteroaryl" is intended to denote an aromatic (unsaturated), 5- or 6-membered, ring, which may be a single ring (e.g. pyridyl) or fused with other 5- or 6-membered rings (e.g. quinoline or indole).

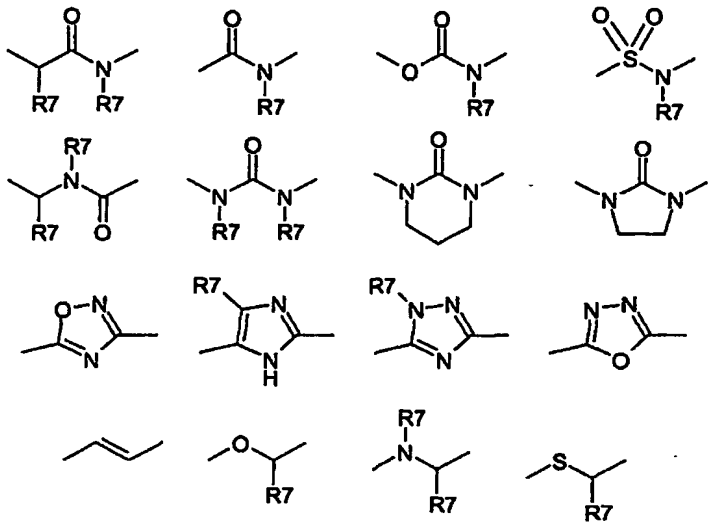
The term "heterocyclyl" is intended to indicate a cyclic unsaturated (heteroalkenyl), aromatic ("heteroaryl") or saturated ("heterocycloalkyl") group comprising at least one heteroatom.

The present invention relates to a compound with the following structure (Formula I)

A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



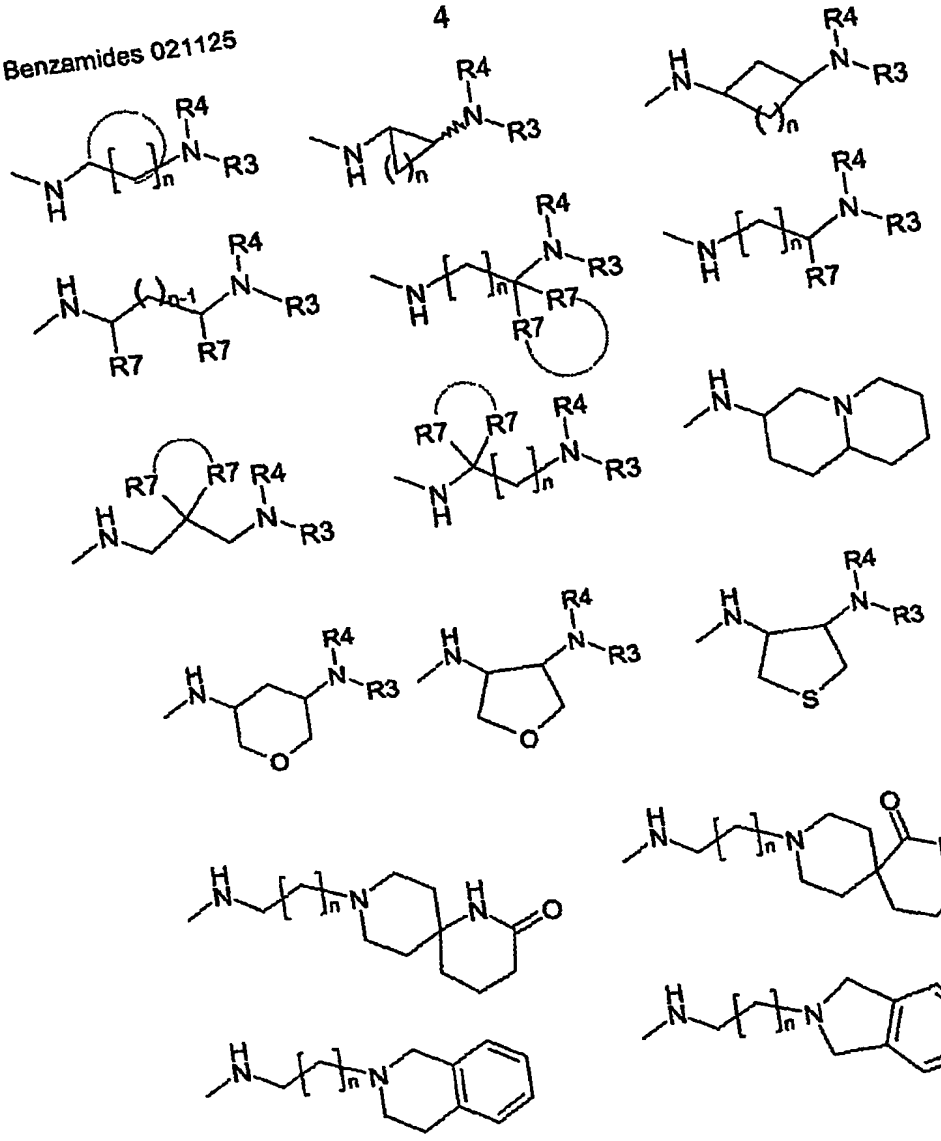
and, wherein the linker may be attached via either of the two free bonds to the Ar1 group;

and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

Ar_1 is an aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 is hydrogen or a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon, and in the case of R1 being ethoxy or propoxy it may be annelated with the benzene ring;

R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbons; alkylcycloalkyl with 4-9 carbons atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, -$CONAlk_2$, or fused moieties such as -O-CH_2-O-, -N=CH-NH-, -O-CH=N-, -N=CH-CH=CH- ; examples of more complex motifs are



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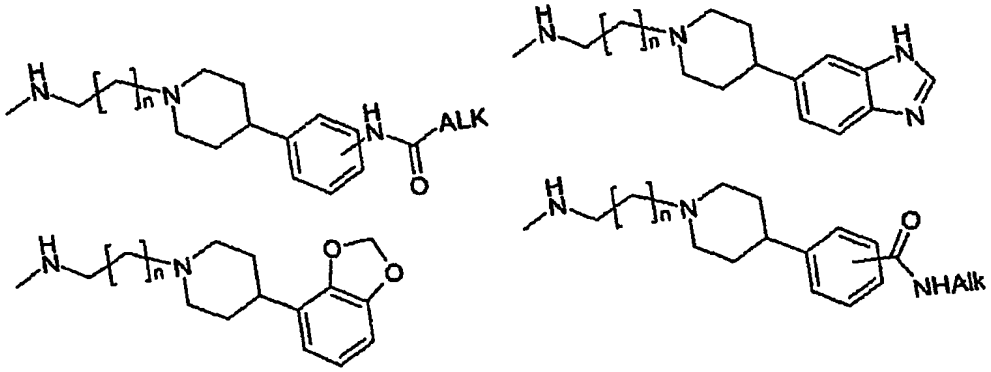
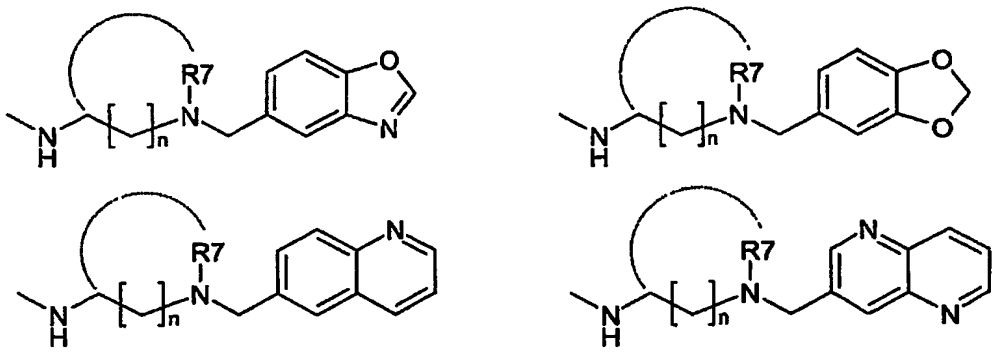




Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 or R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 may the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3; -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

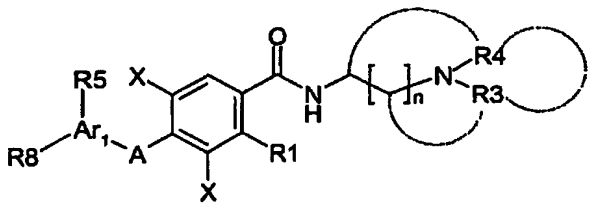
R8 is hydrogen, halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), arylamino groups (ArNR7-, ArNH-), arylalkylamino groups (ArAlkNH-, ArAlkNR7-,ArCH2NR7-,ArCH2NH-), alkoxy groups (AlkO-), alkylamino groups (AlkNH-) dialkylamino groups (Alk_2N-), -$CONH_2$, -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -CF_2-Ar, -$N(CF_3)_2$, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3;

more than one R5 group, same or different, may be present on Ar1; when more than one R5 or when one R5 and one R8 group are present they could be connected to each other, directly or with a suitable connecting moiety, to form rings. For example, a vinyl group could be joined with an amine group on a phenyl to form an indole system; a methoxy group could be joined with a phenol group to form a metylendioxyaryl system;;

X being the same or different H, F, Cl, Br, I, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; OCH_3 or lower alkyl or alkenyl group;

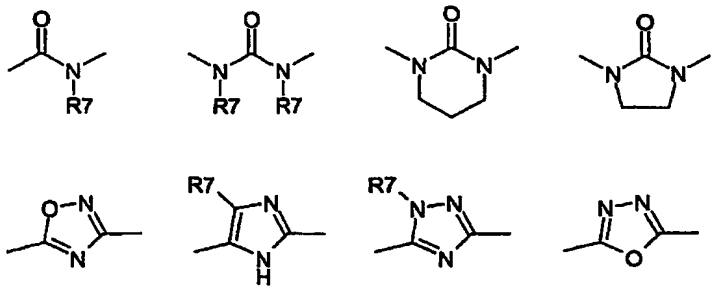
n is 1,2 or 3, and the alkyl chain connecting the amide nitrogen and the aliphatic nitrogen may optionally be substituted with one or more R7, alkyl or heteroalkyl groups, which optionally may form a ring;

In another embodiment, the invention relates to a with the following structure (Formula Ia)



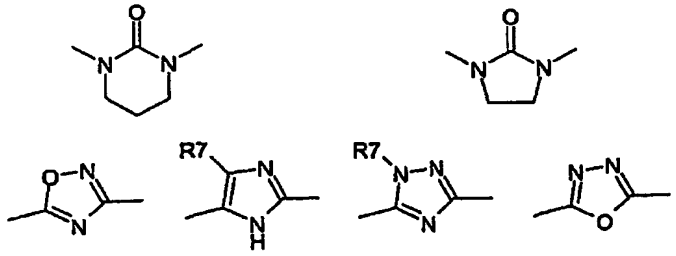
wherein Ar_1, A, B, R1, R3, R4, R5, R8, n and X are as defined above.

-A- may be selected from the group consisting of



or from the group consisting of

Furthermore, the –A- moiety may be selected from the group consisting of



In specific embodiments, R8 is hydrogen, halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3.

Alternatively, R8 is aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups, alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), arylamino groups (ArNH- or ArNR7), arylalkylamino groups (ArAlkNH-, ArAlkNR7-,ArCH2NR7-,ArCH2NH-), -CONHAr, -NHCO-Ar, CF_2-Ar or -CO-Ar.

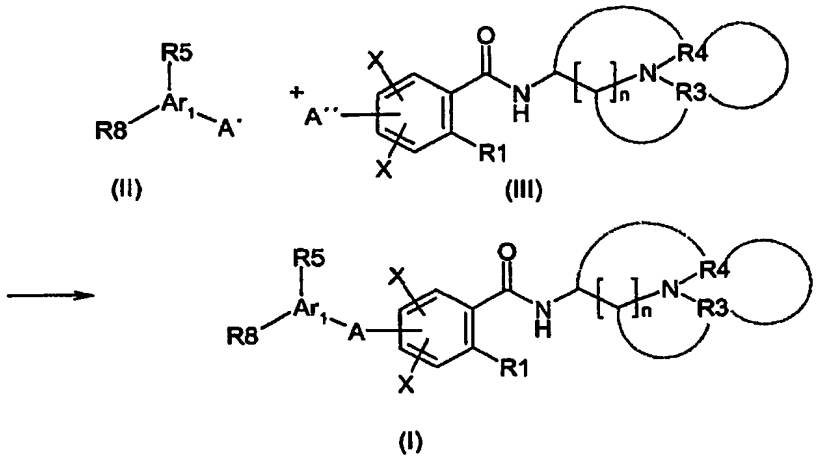
Ar_1 may be an aryl or heteroaryl group such as, e.g. phenyl, pyridine, thiophene, and X is H, F, Cl, Br, I, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3, OCH_3, or Alk. In a specific embodiment X is H, F, Cl or lower alkyl.

R5 may be selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

Other specific embodiments appear from the appended claims and the examples herein.

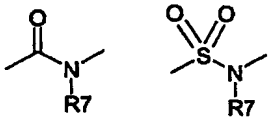
Synthetic routes

Compounds of formula I are preferably made by connecting an appropriately functionalised (A'') benzamide moiety III with a suitably functionalised (A') aryl moiety II using well-known synthetic routes according to the following general scheme (Route 1):



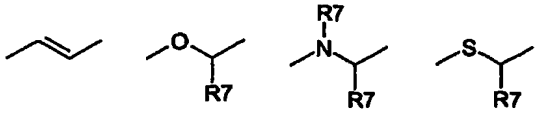
For example, urea bonds -A- can be formed by reaction of II having A' as isocyanate with III having A'' equal to NH-R7 using appropriate catalysis by base or acid. The reverse use of III having A'' as isocyanate with II having A' equal to NH-R7 can also be applied. Analogously, carbamates can for example be made by reaction of II having A' as isocyanate with III having A'' equal to OH or the reverse use of OH and isocyanate in A' and A''.

Preparation of amide and sulphonamide bonds



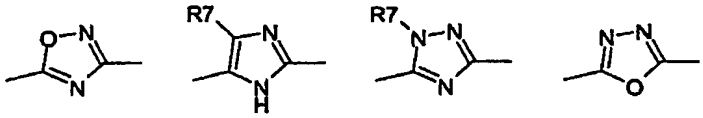
in the connecting A-linkage can be made via reaction of A'' in compound III being NH-R7 with activated forms, e.g. acid chlorides or active esters, of A' in compound II being COOH or SO_2OH. Alternatively, the conversion can be made directly with the acids having A' as COOH using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), and promoters such as 1-hydroxybenzotriazole. The reverse use of A' and A'' in II and III can be applied as well to form the linker in the opposite direction.

Formation of the connecting A-linkage to form

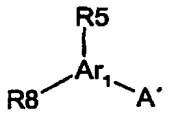


bonds in either direction between Ar1 and the benzamide can be made by N-, O- or S-alkylations of compound II with A′ being OH, NH-R7, or SH with compound III with A′′ being a CH_2-L wherein L being a suitable leaving group such as halogen (Cl, Br, I), tosyl or mesyl using appropriate catalysts and conditions. The alkene linkage can be made by a Wittig reaction with compound II with A′ being CHO and compound III with A′′ being CH_2-PPh_3. The reverse use of A′ and A′′ in II and III can be applied as well to form the linker in the opposite direction.

The 5-membered heterocyclic linkers



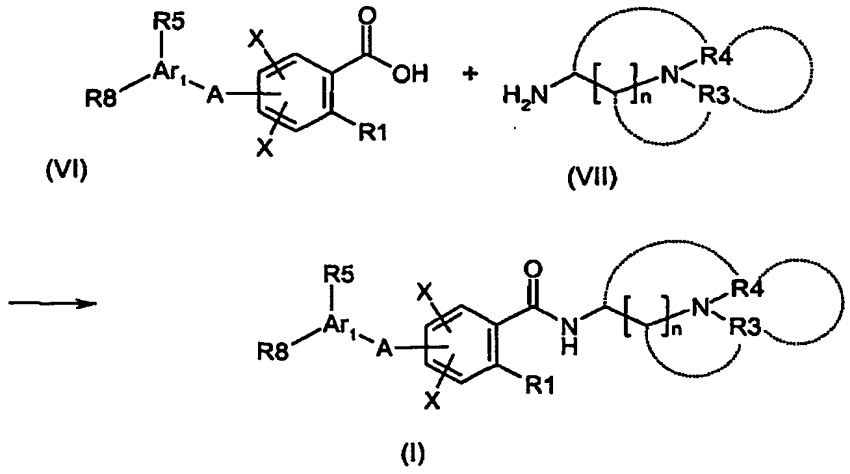
can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made from II with A′ being acylhydrazide with III with A′′ being amide or thioamide or the reverse orientation of A′ and A′′. 1,2,4-Oxadiazole can be formed from II with A′ being amidoxime with III with A′′ being carboxylic ester or the reverse orientation of A′ and A′′. 1,3,4-Oxadiazole can be formed from II with A′ being acylhydrazide with III with A′′ being carboxylic ester or the reverse orientation of A′ and A′′.



(II)

Aromatic substituents R4, R5 and R8 are preferably introduced prior to formation of the A- or B-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

Compounds of formula I are also obtained by connecting carboxylic acid derivatives VI with amines VII using well-known synthetic routes according to the following general scheme (Route 2):

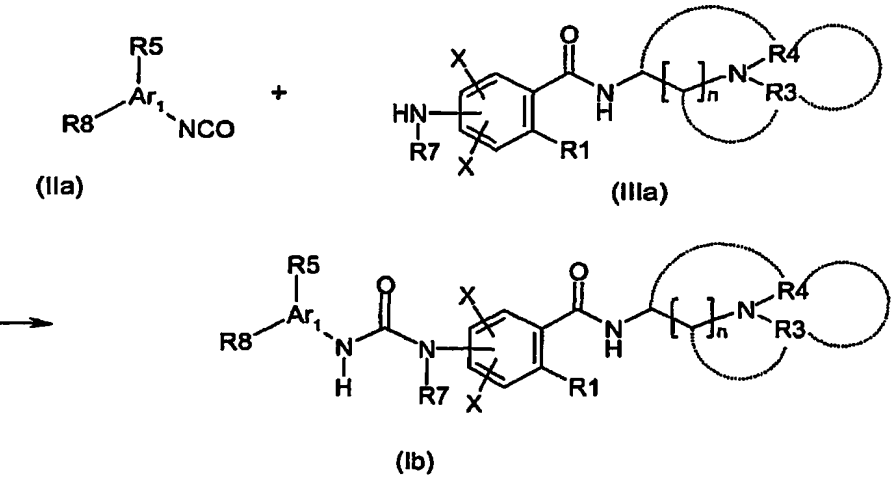


Thus, the benzamide bond is formed by reacting a suitably activated carboxylic acid VI (e.g. acid chloride) with the corresponding amines VII in the presence of a base or using suitable coupling reagents such as DCC in presence of promoting agents and a suitable base.

Alternatively, compounds of formula I can be made by N-alkylation of compounds of formula I having R3 and R4 being hydrogen using well-known synthetic routes such as reductive alkylation or alkylation with alkyl halides in case the functionalisation of the molecule is compatible with this type of reactions (Route 3).

Synthetic method 1A

Thus, compound (Ib) having NHCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.

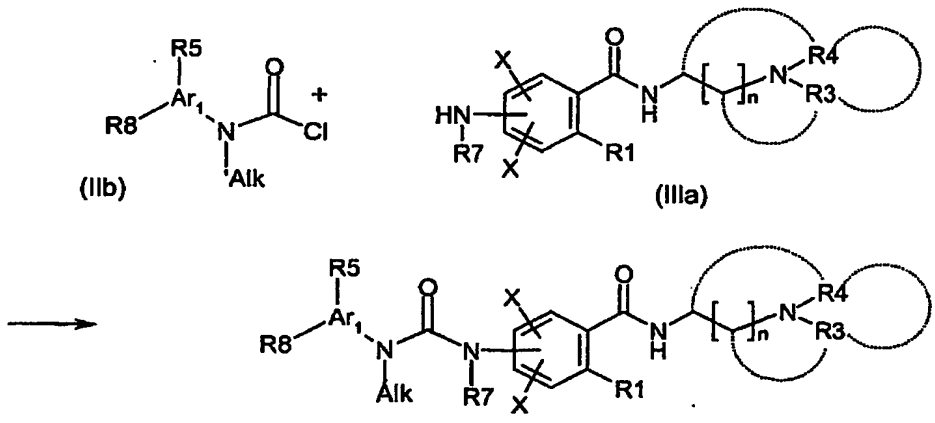


Compound IIa and compound IIIa are reacted in an inert solvent in accordance with standard procedures. Typically, inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. Reaction temperature is usually room temperature and the reaction time is 2 hours to 1 day.

Compound IIa can be produced from the corresponding carboxylic acid. For instance, 4-phenoxyphenylisocyanate can be produced in accordance with methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley); R.C. Larock.

Synthetic method 1B

Compound Ic having N-AlkCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.

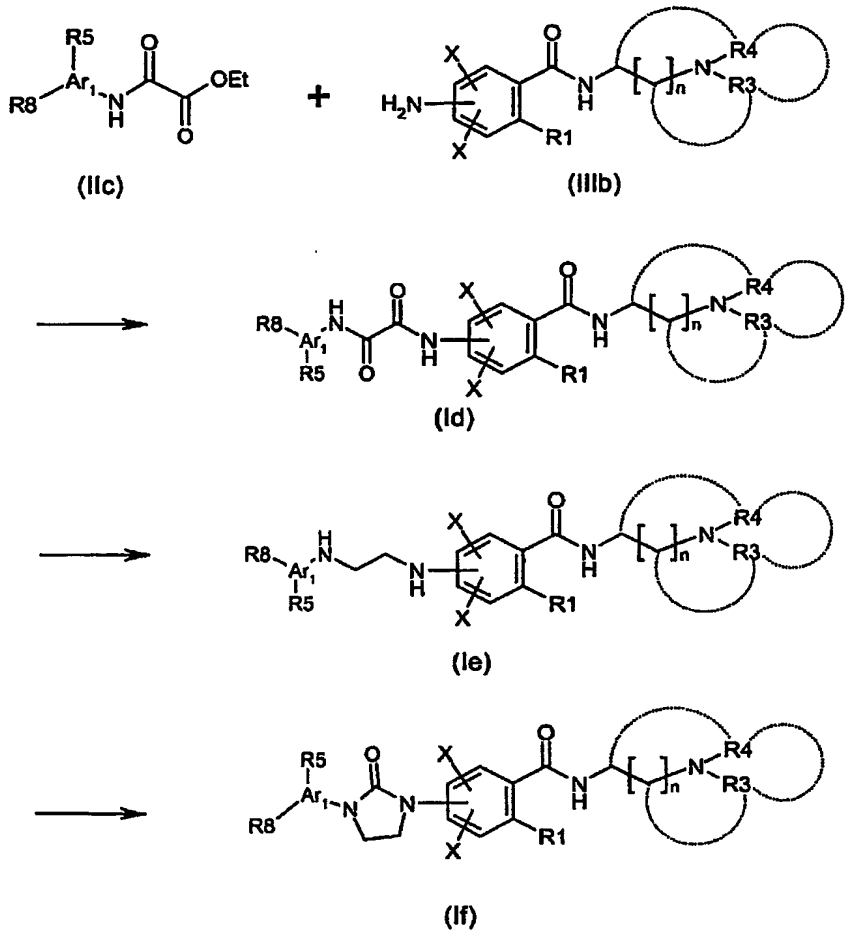


Compound IIIa and 1 equivalent of compound IIb are reacted in an inert solvent in the presence of an excess of a base in accordance with known procedures (e.g. WO 9205174; *J.Med.Chem.* 43(20), 3653-3664, 2000). Suitable inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. As a base can be used for instance triethylamine, diisopropylethylamine and sodium carbonate. Typically, the reaction temperature is 0 °C to room temperature and the reaction time is 1 hour to 1 day.

Compound IIb can be produced from the corresponding N-alkyl aromatic amine by well-known methods. For instance, N-methyl-N-4-phenoxyphenylcarbamoyl chloride can be produced in accordance with methods such as described in *J. Labelled Compd. Radiopharma* 29(2), 149-155, 1991.

Synthetic method 1C

Compound If having 5-membered ring urea as linker A can be produced, for instance, by the following reaction sequence.

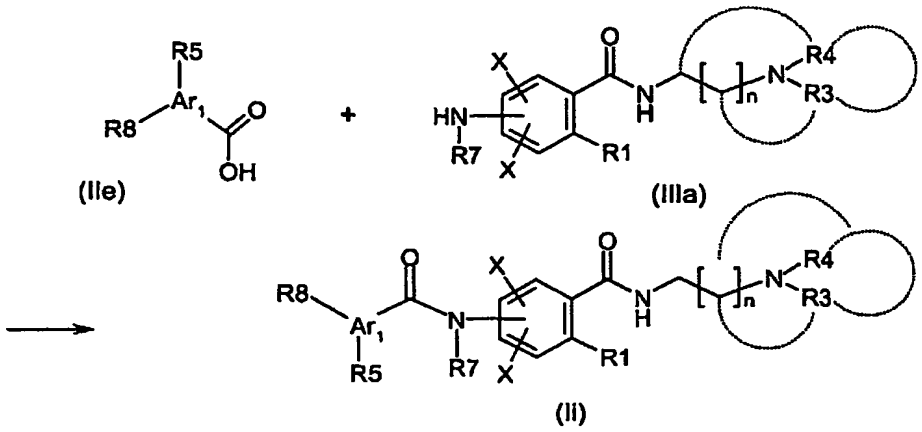


Compound Ie and 1 equivalent of carbonyldiimidazole are reacted in an inert solvent at elevated temperature until the reaction is completed. Typically, the reaction is conducted at reflux in acetonitrile for less than 24 hours.

Compounds IIc, Id and Ie can be produced following the functional group conversions described in procedures like the one in *J.Med.Chem.* 43(20), 3653-3664, 2000.

Synthetic method 1D

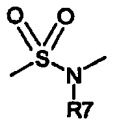
Compound Ii having CON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced by the following amidation reaction.



The amide bonds are formed by reacting a suitably activated carboxylic acid IIe (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with anilines IIIa in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylaminopyridine (DMAP) and sodium carbonate. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed directly from IIe using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

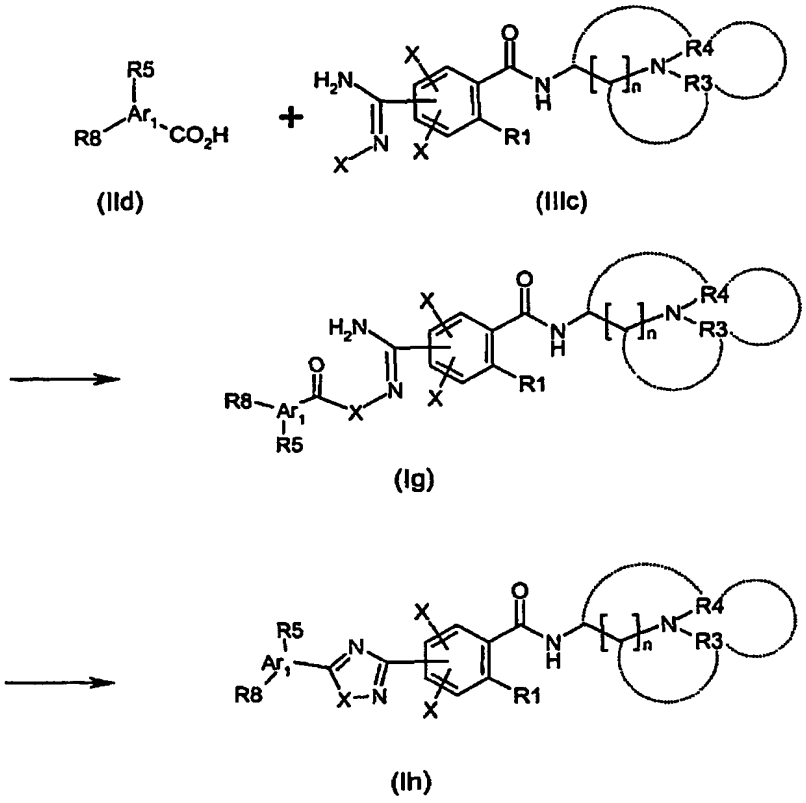
Analogously, a sulphonamide group, as the connecting A-linkage to form



bonds can be made via the corresponding reaction of Ar-NH-R7 (IIIa) with activated forms of sulphonic acids, such sulphonyl chlorides, in the presence of base.

Synthetic method 2

Compound Ih having 1,2,4-oxadiazole (X=O) or 1,2,4-triazole (X=NH) heterocyclic rings as linker A can be produced, for instance, by the following cyclodehydratation reaction.



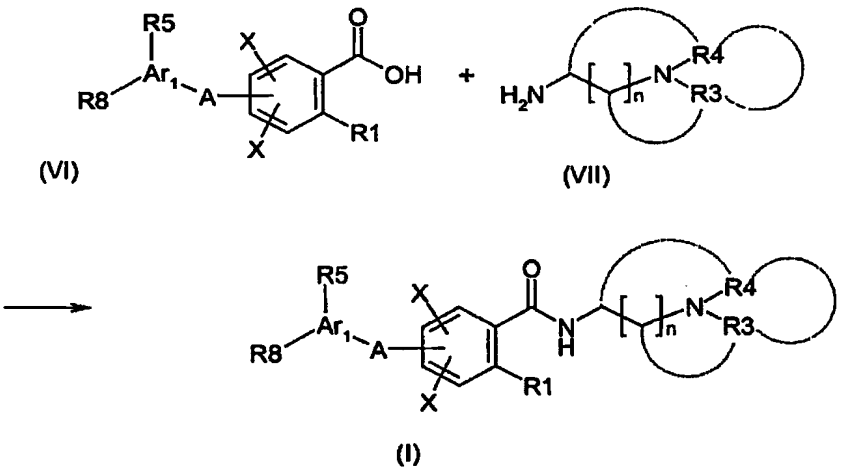
Compound Ig is reacted in an inert solvent with or without the presence of a suitable base or acid (e.g. N-tetrabutyl ammonium fluoride, sodium hydride, sodium ethoxide or polyphosphoric acid) in accordance with standard methods such as described in *Tetrahedron Lett.* 42, 1441-1443, 2001; *Tetrahedron Lett.* 42, 1495-1498, 2001. Suitable, inert solvents can be ether solvents, amide solvents and aromatic solvents. The reaction temperature is usually room temperature to 100°C and the reaction time is 1 hour to 3 days.

Compound Ig can be produced by reacting an activated derivative of compound IId with 1 equivalent of compound IIIc in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine and sodium carbonate.

Appropriate examples of the activated derivatives of compound IId include active esters (e.g. esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinamide), acid chlorides, symmetrical or unsymmetrical anhydrides and orthoesters. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Compound IIIc can be produced from the corresponding amino compound IIIb by well known methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock; In "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky).

Synthetic method 3



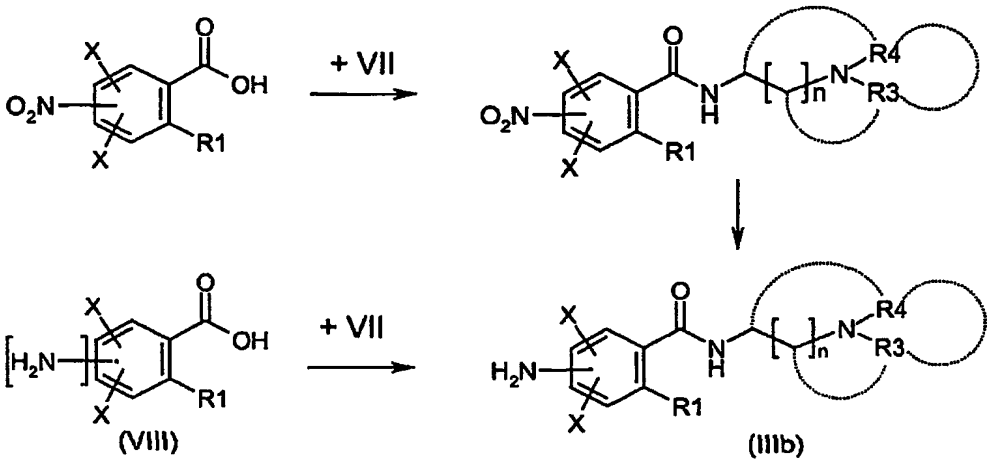
Benzamide bonds are formed by reacting a suitably activated carboxylic acid VI (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with the corresponding amines VII in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylamino-pyridine (DMAP) and sodium carbonate. . The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed by using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-

hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Synthetic method 4

Intermediate IIIb



can be prepared by reacting an activated carboxylic acid derivative VIII according to methods described above, preferably having the aniline nitrogen suitably protected (e.g. Boc, CF_3CO), with the corresponding amine VII. The nitrogen may also be masked as a nitro group that subsequently is reduced to form IIIb. The N-alkylated derivative IIIa may be obtained via reductive alkylation of IIIb.

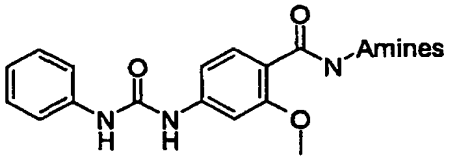
The carboxylic acids VIII are produced by well-known organic reactions including electrophilic substitutions or organometallic reactions such as ortho-lithiation and halogen-metal exchange followed by capture with electrophilic reagents. Alternatively, the aniline nitrogen may be introduced by a benzyne reaction.

Compounds

Below follows some examples of specific compounds according to the invention. In the compounds mentioned, one part of the molecule such as e.g. the amine group, the linker –A-, the Ar_1 group, the R1, R4, R5, R8 group or the chain length is varied, while the other parts are conserved. Though not shown nor specifically mentioned, the invention also

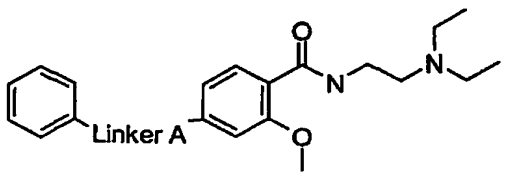
includes all compounds wherein all variations in one part of the molecule, e.g. linker –A- is combined with all variations in another of the features, e.g. variation in the Ar_1 group.

Variation of the amine



2-Methoxy-4-[3-phenyl-ureido]-*N*-(3-pyrrolidin-1-yl-propyl)-benzamide,
N-(4-Dimethylamino-butyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dipropylamino-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-{3-[4-(3-Isobutyrylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-(1-Benzo[1,3]dioxol-5-ylmethyl-piperidin-4-yl)-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-[1-(4-Acetylamino-benzyl)-piperidin-4-yl]-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-[1-(3-Acetylamino-benzyl)-piperidin-4-yl]-2-methoxy-4-(3-phenyl-ureido)-benzamide,
2-Methoxy-*N*-[1-(3-methylcarbamoyl-benzyl)-piperidin-4-yl]-4-(3-phenyl-ureido)-benzamide,
N-{3-[(4-Acetylamino-benzyl)-ethyl-amino]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-{2-[(4-Acetylamino-benzyl)-ethyl-amino]-ethyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-[2-(Benzo[1,3]dioxol-5-ylmethyl-ethyl-amino)-ethyl]-2-methoxy-4-(3-phenyl-ureido)-benzamide,

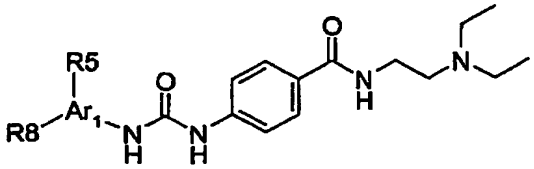
Variation of the linker A



N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzoylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzoyl)-amino]-benzamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(phenyl)-terephthalamide,

N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(phenyl)-terephthalamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzenesulfonylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzenesulfonyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfamoyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[1,3-dimethyl-3-(phenyl)-ureido]-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-imidazolidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-methyl-3-(phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-tetrahydro-pyrimidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(phenyl)-[1,2,4]oxadiazol-5-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-4*H*-imidazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-1*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,3,4]oxadiazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-2*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-5*H*-imidazol-4-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-vinyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenoxymethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzyloxy)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[(phenylamino)-methyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{[methyl-(phenyl)-amino]-methyl}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfanylmethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylsulfanyl)-benzamide

Variation of the aromatic rings as well as their substituents

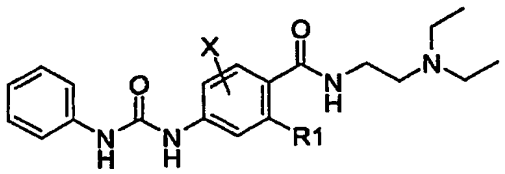


4-[3-(phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(5-indolyl)-ureido]-benzamide,
4-[3-(4-Benzofuranyl)-ureido]-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[3-pyridinyl]-ureido}-benzamide,
4-(3-[2,2']Bipyridinyl-6-yl-ureido)-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(pyridin-3-yloxy)-phenyl]-ureido}-benzamide,

N-(2-Diethylamino-ethyl)-4-{3-(8-quinolinyl)-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(2-phenoxy-pyrimidin-5-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(5-phenoxy-pyrazin-2-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-thiophenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-isothiazolyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-oxazolyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(1*H*-pyrazol-4-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(5-bromo-thiophen-3-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(2-chloro-oxazol-4-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(4-trifuoromethyl-oxazol-2-yl)-ureido]-benzamide,
4-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[3,4-Dichlorophenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[4-Fluoro-5-chlorothiophen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[4-bromo-3-trifluoromethoxy-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[5-(3,4-methylenedioxy-phenoxy)-thiopen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[4-(4-acetamido-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[4-trifluoromethyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-(4-methyl-phenyl)-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-hydroxy-phenoxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-dimethylamino-phenoxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-methylamino-phenoxy)-phenyl]-ureido}-benzamide,
4-{3-[4-(4-Cyano-3-chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-{3-[4-Carbamoyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-benzamide,
4-[3-(3-Chloro-4-cyano-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(2-fluoro-3-methoxy-4-acetamido-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-bromo-6-methoxy-4-phenoxy-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-hydroxymethyl-4-trifluoromethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-carboxamido-4-iodo-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-(*N,N*-dimethylcarboxamido)-4-chloro-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-trifluoromethyl-pyridin-2-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-trifluoromethoxy-thiophen-2-yl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-phenoxy-4-trifluoromethoxy-phenyl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-4-[3-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-7-yl)-ureido]-benzamide,
4-[3-(3-Chloro-4-trifluoromethyl-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[3-(3-phenoxy-4-trifluoromethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[3-(phenyl-trifluoromethyl-amino)-phenyl]-ureido}-benzamide,

Substituents on the benzamide moiety



N-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-phenyl-ureido]-benzamide,
5-Fluoro-4-(3-phenyl-ureido)-2,3-dihydro-benzofuran-7-carboxylic acid (2-diethylamino-ethyl)-amide,
4-(3-Phenyl-ureido)-2,3-dihydro-benzofuran-7-carboxylic acid (2-diethylamino-ethyl)-amide,
N-(2-Diethylamino-ethyl)-5-fluoro-2-methoxy-4-(3-phenyl-ureido)-benzamide,
N-(2-Diethylamino-ethyl)-2-ethoxy-5-fluoro-4-(3-phenyl-ureido)-benzamide,
N-(2-Diethylamino-ethyl)-3-fluoro-4-(3-phenyl-ureido)-benzamide,
3-Chloro-N-(2-diethylamino-ethyl)-4-(3-phenyl-ureido)-benzamide.

Salts, complexes or solvates

The invention also relates to physiologically acceptable salts, complexes, solvates or prodrugs of the compounds of the invention.

When a compound of the invention possesses a basic functional group it can form a salt with an inorganic or organic acid.

Examples of physiologically acceptable salts of the compounds according to the invention include salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid (to form e.g. a nitrate or a nitrite), sulfuric acid (to form

e.g., a H_2SO_3 salt, a sulfate or a H_2SO_5 salt) and phosphoric acid (to form e.g. a H_3PO_3 salt or a H_3PO_4 salt)

Examples of salts with organic acids include salts with formic acid, acetic acid, propionic acid, butyric acid, pentanoic acid, oxalic acid, tartaric acid, malonic acid, succinic acid, citric acid, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, acrylic acid, malic acid, fumaric acid, H_2CO_3, lactic acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 3-chlorobenzoic acid.

Examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Optical isomers

When a compound of the invention contains optical isomers, diastereomers or other stereroisomers these are included as a compound of the invention as well as the racemate, i.e. mixture of enantiomers. Each of them can be obtained by methods known by a person skilled in the art. For example the optical isomer can be obtained using an optically active synthetic intermediate, an asymmetric synthesis or subjecting the racemic mixture of the final product or a suitable intermediate to optical resolution in accordance with known methods such as, e.g., fractional recrystallisation method, chiral column method, diastereomer method etc.

Other forms

The invention also encompasses a compound in amorphous, any polymorphous or any crystalline form.

Disorders

The compounds according to the invention can be used in medicine and modulate the activity of a MCH receptor. The compounds may be used as agents for preventing or treating diseases caused by or involving a melanin-concentrating hormone, i.e. they are useful for treating or preventing a MCH or MCH receptor related disorder or abnormality in a subject such as, e.g., an animal or a mammal such as, e.g., a human.

The compounds according to the invention may have antagonistic, inverse agonistic, agonistic or allosteric activity against a MCH receptor, normally antagonistic activity.

In the present context an agonist is defined as a compound that increases the functional activity of a MCH receptor (e.g. the signal transduction through a receptor). The term "agonist" includes partial agonist, i.e. which increases the functional activity of the receptor to a submaximal level. An inverse agonist (or negative antagonist) is defined as a compound that decreases the basal functional activity of a MCH receptor. An allosteric compound is defined as a compound that enhances or diminishes the effects of other receptor ligands.

An antagonist is defined as a compound that decreases the functional activity of a MCH receptor either by inhibiting the action of an agonist or by its own intrinsic activity.

The MCH receptors mentioned in the invention include MCH1 and MCH2 receptors. It also includes MCH receptors having at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequences CTLITAMDAN or CTIITSLDTC.

The MCH receptors may be an animal or a mammalian or non-mammalian receptor, such as a human receptor.

Increasing or decreasing the activity of a MCH receptor such as, e.g. a MCH1 receptor alleviates a MCH-related disorder or abnormality. In specific embodiments the disorder is a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, a muscoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as, e.g., Alzheimer's disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as, e.g. Parkinson's disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as, e.g. depression, a stress-related disorder, a fluid-balance disorder, a urinary disorder such as, e.g., urinary incontinence, a seizure disorder, pain, psychotic behaviour such as, e.g., schizophrenia, morphine or opioid tolerance, opiate addiction or migraine.

More specifically, the compounds of the invention are useful for the treatment or prevention of feeding disorders such as, e.g., overweight, adiposity, obesity and bulimia (e.g. malignant mastocytosis, exogeneous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adposity, hypoplasmic obesity, hypophysal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity etc.), hyperfagia, emotional disorders, dementia or hormonal disorders.

In the present context the term body mass index or BMI is defined as body weight (kg)/height^2 (m^2), and the term overweight is intended to indicate a BMI in a range from about 25 to about 29.9, whereas obesity is intended to indicate a BMI, which is at least about 30.

A compound of the invention is also useful as an agent for preventing or treating lifestyle diseases such as, e.g., diabetes, diabetic complications (e.g. retinopathy, neuropathy, nephropathy etc.), arteriosclerosis and gonitis.

The present invention further relates to a cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to the invention

The invention also relates to a method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A mentioned above, the MCH-related disorders may be a feeding disorder. Accordingly, the invention relates to a method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

The invention also relates to a method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Furthermore, the invention relates to a method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Another aspect of the invention is a method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A still further aspect of the invention is a method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Pharmaceutical compositions

The compounds for use in the methods according to the invention are normally presented in the form of a pharmaceutical or a cosmetic composition comprising the specific compound or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

The compounds may be administered to the animal including a mammal such as, e.g., a human by any convenient administration route such as, e.g., the oral, buccal, nasal, ocular, pulmonary, topical, transdermal, vaginal, rectal, ocular, parenteral (including *inter alia* subcutaneous, intramuscular, and intravenous), route in a dose that is effective for the individual purposes. A person skilled in the art will know how to chose a suitable administration route.

The pharmaceutical or cosmetic composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.

A semi-solid form of the composition may be a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or a aerosol.

Fluid compositions, which are sterile solutions or dispersions can utilized by for example intraveneous, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection of infusion. The compounds may also be prepared as a sterile solid composition, which may be dissolved or dispersed before or at the time of administration using e.g. sterile water, saline or other appropriate sterile injectable medium.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be vagitories, suppositories, plasters, patches, tablets, capsules, sachets, troches, devices etc.

The dosage form may be designed to release the compound freely or in a controlled manner e.g. with respect to tablets by suitable coatings.

The pharmaceutical composition may comprise a therapeutically effective amount of a compound according to the invention.

The content of a compound of the invention in a pharmaceutical composition of the invention is e.g. from about 0.1 to about 100% w/w of the pharmaceutical composition.

The pharmaceutical or cosmetic compositions may be prepared by any of the method well known to a person skilled in pharmaceutical or cosmetic formulation.

In pharmaceutical or cosmetic compositions, the compounds are normally combined with a pharmaceutical excipient, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically or cosmetically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavours, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Dosage

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the composition, the route of administration, the frequency of administration, the age, weight, gender, diet and condition of the subject to be treated and the condition being treated and the advancement of the disease condition etc.

Suitable dosages may be from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

The amounts can be divided into one or several doses for administration daily, every second day, weekly, every two weeks, monthly or with any other suitable frequency. Normally, the administration is daily.

A compound or a pharmaceutical composition according to the invention may be used in combination with other drug substances such as agents for treating disorders like e.g. diabetes, diabetes complications, obesity, hypertension, hyperlipidemia, arteriosclerosis, arthritis, anxiety, and/or depression etc.

Experimental

Materials and methods

Transfections and Tissue Culture - The cDNA encoding the human MCH-1 receptor was cloned from a human brain cDNA library and cloned into the eukaryotic expression vector pcDNA3.1 (Invitrogen). Assays were performed on transiently transfected COS-7 cells or stably transfected CHO (Chinese Hamster Ovary) cells, expressing the human MCH-1 receptor in pcDNA3.1. Stable MCH-1 receptor transfectants of CHO cells were obtained using 5 μg plasmid cDNA and a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) with subsequent selection in 1 mg/ml G418 (Life Technology). Clones were screened by a MCH receptor radioligand binding assay (as described below). Stably transfected CHO cells were maintained in RPMI 1640 culture medium (Invitrogen), supplemented with 10 % fetal calf serum (Invitrogen), 100 U/ml penicillin, 100 μg/ml streptomycin (Life Technology), and 500 μg/ml G418 (Life Technology). COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 (Invitrogen) supplemented with 10 % fetal calf serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and were transiently transfected by a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) two days before assay.

Radioligand Binding Assay -Transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor were seeded in multi-well culture plates one day before the assay. The number of cells per well was determined by the apparent expression efficiency of the cell line aiming at 5 - 10 % binding of the added radioligand. Cells were assayed by competition binding for 3 hours at room temperature using 15 pM [^{125}I]-MCH (Amersham Pharmacia Biotech) plus variable amounts of unlabeled ligand in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, supplemented with 10 mM $MgCl_2$, 5 mM $MnCl_2$, 10 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 100 µg/ml bacitracin. The assay was performed in duplicate. Nonspecific binding was determined as the binding in the presence of 1 μM MCH (Bachem). Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the dissociation and inhibition constants (K_d and K_i) were estimated from competition binding using the equations $K_d=IC_{50}-L$ and $K_i=IC_{50}/(1+L/K_d)$, respectively, where L is the concentration of radioligand.

Phosphatidylinositol assay - To assay phosphatidylinositol turnover, transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor ($2x10^5$ cells/well) were incubated for 24 h with 5 μCi of [^{3}H]-*myo*-inositol (Amersham Pharmacia Biotech) in 0.5 ml inositol-free culture medium. Cells were washed

twice in PI-buffer: 20 mM HEPES, pH 7.4, supplemented with 140 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 10 mM glucose, 0.02% (w/v) bovine serum; and were incubated in 0.5 ml PI-buffer supplemented with 10 mM LiCl at 37 °C for 45 min. Phosphatidylinositol turnover was stimulated by submaximal concentrations of MCH, i.e. 10 nM in the presence of increasing amounts of ligand. The ligand was added 5 min. before adding the agonist (MCH). Cells were extracted with 10 mM ice-cold Formic acid, and the generated [^{3}H]-inositol phosphates were purified on Bio-Rad AG 1-X8 anion-exchange resin. Determinations were made in duplicate. PI data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego).

Scintillation Proximity Assay (SPA)– Measurement of [^{125}I]-MCHbinding was performed in duplicates by incubating membranes and beads with tracer in the presences of various concentrations of test compounds (10^{-8} to 10^{-4} M) in DMSO (3 µl) at room temperature for two hours. Membranes and beads were pre-incubated for 20 min. The binding buffer contained 50 mM Tris (pH 7.4), 8 mM MgCl2, 12% glycerol, 0.1% (w/v) bovine serum albumin (BSA), and protease inhibitors (Complete protease inhibitor cocktail tablets, Roche). A final [^{125}I]-MCH(2000 Ci/mmol; Amersham Pharmacia Biotech) concentration of 75.000 cpm/well (33.8 nCi) was applied and PEI-treated WGA-coupled PVT SPA beads, type B from Amersham Pharmacia Biotech were used at a final concentration of 0.4 mg/well. Moreover, CHO-K1 membranes expressing the hMCHreceptor were purchased from Euroscreen (ES-370-M) and a final concentration of 2µg/well were used. Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the inhibition constant (K_i) were estimated from competition binding using the equation $K_i=IC_{50}/(-1+L/K_d)$, where L and K_d are the concentration and affinity constant, respectively, of the radioligand.

In Vivo model measuring effects on food intake - The effects of test compounds on food intake were studied in male Sprague Dawley rats (290 – 325 g). The animals were individually housed in plexiglas cages (370 cm^2) at room temperature (21 ± 2 °C)and maintained on a 12 : 12h light – dark cycle (08.00 h – 20.00 h dark). They had free access to water; food (normal rat chow) was only available for the first 6 h of the dark period. The actual experiments studying food intake were conducted when the animals were well accustomed to the housing conditions and feeding paradigm. At least a 10 – day acclimatization period was observed after entrance of the animals in the facilities.

At a day of an experiment, weight matched groups (n = 6-7) were injected with one of the test compounds (i.p. 10 mg/kg, dissolved in 10 % Tween 80), or the solvent (10 % Tween 80, 2 ml/kg). Cumulative food intake was registered over the 6-h feeding period. Results were analyzed by one-way ANOVA followed by post hoc Bonferroni test.

References:

Gether, U., Marray, T., Schwartz, T.W., and Johansen, T.E. (1992). Stable expression of high affinity NK_1 (substance P) and NK_2 (neurokinin A) receptors but low affinity NK_3 (neurokinin B) receptors in transfected CHO cells. *FEBS Lett.*, 296, 241-244.

Johansen, T.E., Schøller, M.S., Tolstoy, S. and Schwartz, T.W. (1990). Biosynthesis of peptide precursors and protease inhibitors using new constitutive and inducible eukaryotic expressions vectors. *FEBS Lett.*, 267, 289-294.

Examples

***General comments*:**

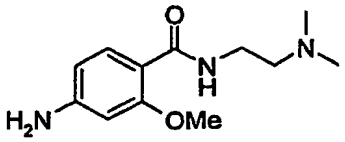
A variety of unsymmetrically amines as in example 77 has been synthesised according to the following literature description, *Amundsen, L. H., Sanderson, J. J., Organic Syntheses, Vol.3, 256* Substitued diarylethers and diarylamines that has been used for urea couplings has been sythesised from arylhalides and phenols *(Buck, E., Song, Z. J., Tschaen, D., Dormer, P. G:, Volante, R. P., Reider, P. J., Organic Lett., 2002, 4, 1623)* or arylboronic acids and phenols or anilines *(Evans, D. A., Katz, J. L., West, T. R., Tetrahedron Lett. 1998, 39, 2937 and Chan, D. M. T., Monaco, K. L., Wang, R.-P., Winters, M. P., Tetrahedron Lett., 1998, 39, 2933.)*.

^1H NMR data are given either in full detailed or with characteristic selected peaks.
LCMS Conditions I: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Negative ion scanning mode. Named; an20n15
LCMS Conditions II: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Positive ion scanning mode. Named; an20p15
LCMS Conditions III: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 20% MeCN to 95% MeCN over 8 min, then 95% MeCN for 2 min. Positive ion scanning mode. Named; an20p10

LCMS Conditions IV: Unpolar solvent: MeCN w/0.01% formic acid. Polar solvent: H_2O w/0.01% formic acid. Gradient: From 10% MeCN to 95% MeCN over 10 min, then 95% MeCN for 5 min. Positive ion scanning mode. Named; an10p15

Example 1

4-Amino-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide

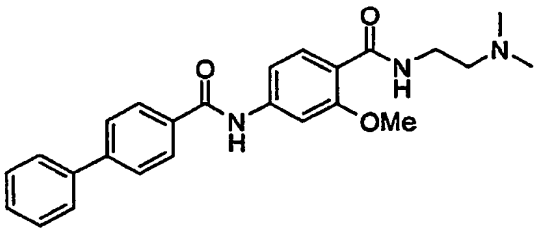


In a flask were placed 4-nitro-2-methoxybenzoic acid (0.50 g, 2.5 mmol) and dichloromethane (10 µl) under nitrogen atmosphere. The solution was cooled to 0°C, whereupon oxalyl chloride (0.20 µl, 2.3 mmol) and *N,N'*-dimethylformamide (2.0 µl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 1h when potassium carbonate (0.25 g, 2.5 mmol) was added followed by addition of *N,N*-dimethylethylenediamine (0.30 µl , 2.5 mmol). The reaction mixture was stirred overnight before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated leaving 0.54 g (79 %) of *N*-(*N,N*-dimethylaminoethylamine)-4-nitro-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H), 2.52-2.60 (m, 2H), 3.52-3.61 (m, 2H), 4.08 (s, 3H), 7.8-7.95 (m, 2H) and 8.29-8.37 (m, 1H).

To a solution of *N*-(*N,N*-dimethylaminoethyl)-4-nitro-2-methoxybenzoic amide (0.50 g, 1.87 mmol) in ethanol (10 µl) was Pd/C (40 mg, 20% w/w) added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo*. The crude product was chromatographed (Al_2O_3, dichloromethane/methanol/ammonia, 200:10:1) giving 0.42 g (95%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 6H), 2.52 (t, 2H), 3.52 (q, 2H), 3.87 (s, 3H), 6.19 (s, 1H), 6.32 (d, 1H), 7.98 (d, 1H) and 8.13 (br s, 1H).

Example 2

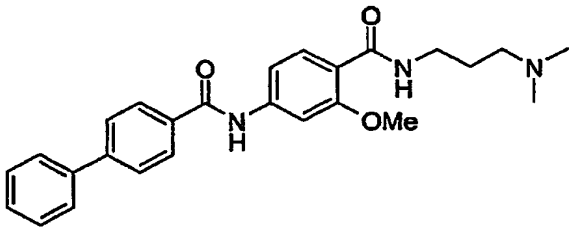
Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-3-methoxy-phenyl]-amide



4-phenyl-benzoic acid (0.35 g, 1.8 mmol) was dissolved in dichloromethane (10 µl) in an inert atmosphere and cooled to 0 °C, whereupon oxalyl chloride (140 µl,1.6 mmol) and *N,N'*-dimethylformamide (5 µl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 1h when potassium carbonate (0.25 g, 1.77 mmol) was added. This solution was slowly added under inert atmosphere to **Ex 1** dissolved in dichloromethane (5 µl) and the reaction mixture was stirred overnight before extraction with EtOAc and Na2SO4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Al2O3, dichloromethane/methanol/ammonia, 200:10:1, followed by EtOAc/Heptane, 1:1) giving 10 mg (14%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 4.04 (s, 3H), 6.96 (d, 1H), 8.36 (br s, 1H).

Example 3

Biphenyl-4-carboxylic acid [4-(3-dimethylamino-propylcarbamoyl)-3-methoxy-phenyl]-amide

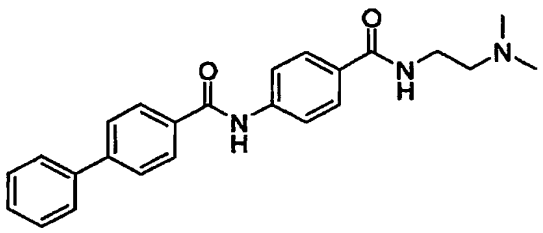


Following the same procedure as described in **Ex 1** was *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide prepared from 2-methoxy-4-nitrobenzoic acid (0.7 g, 3.55 mmol), oxalyl chloride (0.28 µl , 3.2 mmol), triethylamine (0.99 µl, 7.1 mmol) and 3-dimethylaminopropylamine (0.45 µl , 3.55 mmol) followed by reduction with Pd/C (0.04 g, 20% w/w) gave 0.67 g (75%) of *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (t, 2H), 2.24 (s, 6H), 2.36 (t, 2H), 3.49 (m, 2H), 3.90 (s, 3H), 4.02 (br s, 2H), 6.20 (s, 1H), 6.34 (d, 1H), 7.91 (br s, 1H) and 8.02 (d, 1H).

To a solution of 4-biphenylcarbonyl chloride (0.26 g, 0.80 mmol) in dichloromethane (5 µl) under inert atmosphere was a solution of the above prepared compound in dichloromethane (3 µl) added the reaction mixture was stirred at room temperature for three days. The purification was performed according to the protocol for preparation of **Ex 2** and the crude product was chromatographed (Al_2O_3, EtOAc/Heptane, 2:1) giving 0.10 g (30%) of the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (t, 2H), 2.30 (s, 6H), 2.44 (t, 2H), 3.55 (m, 2H), 4.04 (s, 3H), and 6.96 (d, 1H).

Example 4

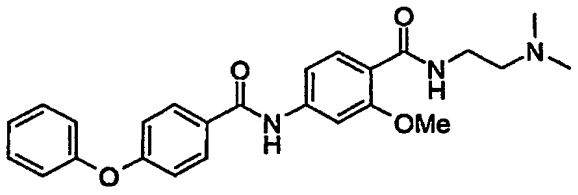
Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-phenyl]-amide



To a solution of 4-nitrobenzoyl chloride (0.50 g, 2.7 mmol) in dichloromethane (10 µl) were triethylamine (0.75 µl , 5.4 mmol) and *N,N*-dimethylethyldiamine added. The reaction mixture was stirred for three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was dissolved in ethanol (10 µl) and Pd/C (40 mg, 20 % w/w) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a celite pad and the filtrate was concentrated *in vacuo* giving 0.32 g (56%) of 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide.
To a solution of 4-biphenylcarbonyl chloride (0.47 g, 2.2 mmol) in dichloromethane (6 µl) under inert atmosphere were added triethylamine (0.4 µl , 2.9 mmol) and 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide (0.3 g, 1.45 mmol) dissolved in dichloromethane (3 µl). The reaction mixture was stirred at room temperature for three days. An additional portion of dichloromethane (3 µl) and PS-trisamine (0.8 g, 3.38 mmol/g) were added to the reaction mixture and the stirring was continued for 2 h at room temperature. The resin was filtered off and rinsed twice with dichloromethane (2 x 3 µL) before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:10:1) and recrystillazed (EtOAc) giving 0.176 g (31%) of the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 2.74 (t, 2H), 4.19 (t, 2H), 7.90 (d, 2H).

Example 5

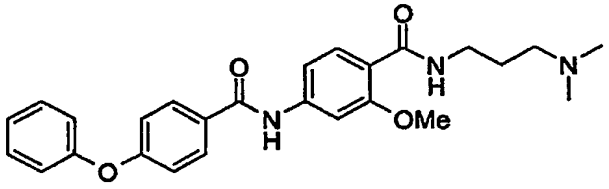
***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**



In a flask were placed 4-phenoxy benzoic acid (27 mg, 0.13 mmol) and *N,N*-dimethylformamide (2 µL) and the flask was cooled to 0°C, whereupon EDAC (24 mg, 0.13 mmol) and HOBt (17 mg, 0.13 mmol) were added. The mixture was gently stirred for 20 minutes at room temperature before **Ex 1** (41 mg, 0.19 mmol) dissolved in *N,N*-dimethylformamide and DiPEA (22 µl, 0.13 mmol) were added. The reaction was continuously stirred three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 12 mg (20%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 6H), 2.77 (m, 2H), 3.68 (m, 2H), 4.03 (s, 3H), 8.16 (d, 1H), and 8.39 (br s, 1H).

Example 6

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**

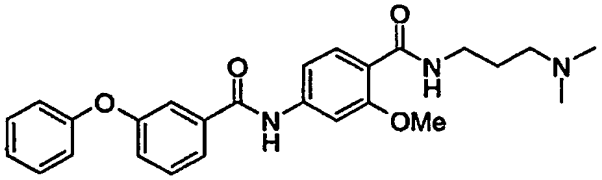


N-(N,N-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 µL), 4-phenoxy benzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 µL). The solvent was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 200:10:1) yielded 8 mg (2%) of the title product. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 1.8 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.53 (q, 2H), 4.02 (s, 3H), 6.91 (d, 1H) and 7.89 (d, 2H).

Example 7

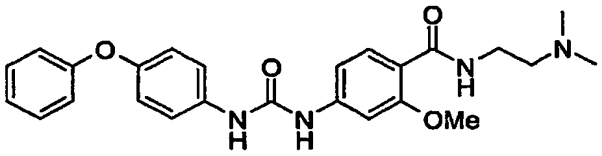
***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(3-phenoxy-benzoylamino)-benzamide**



N-(N,N)-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 μL), 3-phenoxybenzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N-(N,N-*dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 μL). The solvent was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 11 mg (3%) of the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.54 (m, 2H), 4.00 (s, 3H), 6.92 (d, 1H) and 7.99 (d, 1H).

Example 8

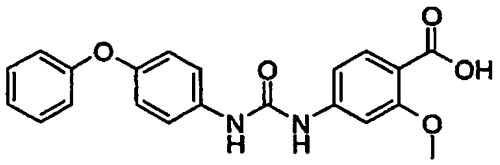
***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



To a solution of **Ex 1** (30 mg, 0.13 mmol) in dichloromethane (2 μL) under nitrogen atmosphere was 4-phenoxyphenylisocyanate (64 μl, 0.30 mmol) added. The reaction was stirred for 2 h at room temperature, whereupon PS-trisamine (100 mg, 4.2 mmol/g). The suspension was gentle stirred over night. Methanol (20 μL) was added to dissolve some precipitation before the resin was filtered off and rinsed with dichloromethane (10 μL). The solvents were removed in vacuo and the crude product was purified through chromatography (silica, dichloromethane/ methanol/ammonia, 100:20:2) giving 24 mg (42%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (t, 2H), 3.54 (m, 2H), 3.90 (s, 3H), 8.52 (s, 1H), 8.67 (s, 1H).

Example 9

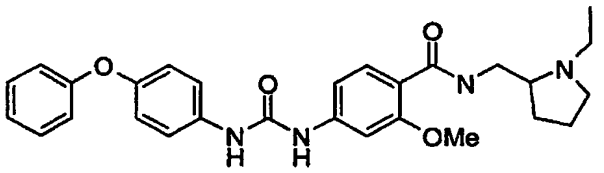
2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzoic acid



To a solution of 4-nitro-2-methoxybenzoic acid (5.0g, mmol) in ethanol (100 µL) was added Pd/C (200 mg, 20% w/w). The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo* giving 4-amino-2-methoxybenzoic acid. To a solution of 4-amino-2-methoxybenzoic acid (0.50 g, 3.0 mmol) in dichloromethane (10 µL) was added 4-phenoxyphenylisocyanate (0.65 µL, 3.6 mmol) under inert atmosphere. The reaction mixture was stirred for three days at room temperature and a precipitate was formed. Filtration gave 1.1 g (97%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.92-7.02 (m, 5H), 7.09 (t, 1H), 7.32-7.42 (m, 3H), 7.48 (d, 2H), 7.66 (d, 1H), 8.79 (s, 1H), and 9.03 (s, 1H).

Example 10

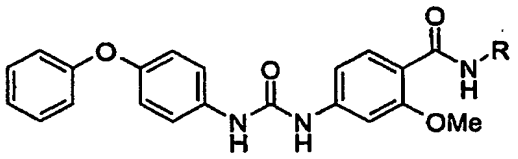
***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



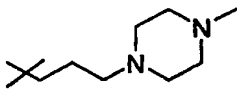
In a flask were placed **Ex 9** (57 mg, 0.15 mmol), HOBt (23 mg, 0.17 mmol), PS-DCC (0.15 g, 1.35 mmol/g), and dichloromethane (2 µL). The mixture was stirred at room temperature for 30 minutes, whereupon 2-aminomethyl-ethylpyrrolidine (0.10 mmol) was added. The reaction mixture was stirred over night. PS-trisamine (140 mg, 0.50 mmol) was added and stirring was continued for a day more. The resin was filtered off and rinsed with dichloromethane (3 x 2 µL). The solvent was removed *in vacuo* giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

Example 11-18

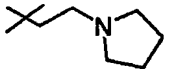
According to the procedure outlined in example 10 were the following compounds prepared utilizing **Ex 9** and the corresponding primary amines to the R-group;



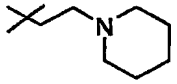
R =



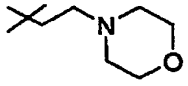
11



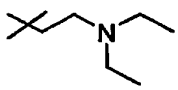
12



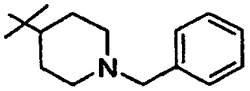
13



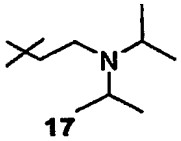
14



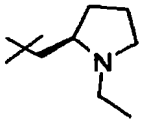
15



16



17



18

Example 11

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 1-(3-aminopropyl)-4-methylpiperazine was coupled giving 43 mg (82%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.60 (d, 1H), 8.69 (s, 1H), 9.02 (s, 1H).

Example 12

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide

Ex 9 and *N*-(2-aminoethyl)pyrrolidine was coupled giving 30 mg (63%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.72 (d, 1H), 8.44 (t, 1H), 8.85 (s, 1H), 9.13 (s, 1H).

Example 13

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-piperidin-1-yl-ethyl)-benzamide

Ex 9 and 1-(2-aminoethyl)piperidine was coupled giving 40 mg (81%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.64 (d, 1H), 7.06 (t, 1H), 7.95 (d, 1H), 8.58 (t, 1H), 8.76 (s, 1H), 9.03 (s, 1H).

Example 14

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 4-(2-aminoethyl)morpholine was coupled giving 18 mg (36%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 6.47 (d, 1H), 7.08 (t, 1H), 8.47 (s, 1H), 8.58 (t, 1H), 8.74 (s, 1H).

Example 15

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and *N,N*-diethyl-ethylendiamine was coupled giving 38 mg (78%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, 6H), 2.70 (q, 4H), 3.86 (s, 3H), 6.73 (d, 1H), 7.05 (t, 1H), 8.55 (t, 1H), 8.89 (s, 1H), 9.19 (s, 1H).

Example 16

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and 4-amino-1-benzylpiperidine was coupled giving 39 mg (70%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (s, 2H), 3.91 (s, 3H), 8.51 (s, 1H), 8.76 (s, 1H).

Example 17

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 8.82 (s, 1H), 9.09 (s, 1H).

Example 18

***N*-(1-Ethyl-pyrrolidin-2*R*-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and (*R*)-2-aminomethyl-ethylpyrrolidine was coupled giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

The following examples were prepared from **Ex 9** according to the same procedure as Ex 10-18

Example 19

***N*-(4-Benzyl-morpholin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.49 (dd, 1H), 7.96 (d, 1H), 8.42 (t, 1H), 8.56 (s, 1H), 8.82 (s, 1H).

Example 20

***N*-(1-Benzyl-pyrrolidin-3-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 6.48 (dd, 1H), 8.40 (d, 1H), 8.60 (s, 1H), 8.87 (s, 1H).

Example 21

***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, 6H), 3.84 (s, 3H), 9.51 (s, 1H), 9.88 (s, 1H).

Example 22

***N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.50 (dd, 1H), 8.65-8.70 (m, 2H), 8.56 (s, 1H).

Example 23

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 24

2-Methoxy-*N*-[3-(2-methyl-piperidin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 25

N-(3-Diethylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 26

2-Methoxy-*N*-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 27

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 6H), 3.87 (t, 3H), 8.21 (t, 1H), 9.17 (s, 1H), 9.53 (s, 1H).

Example 28

***N*-(4-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

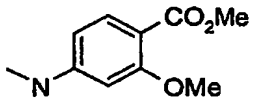
Example 29

***N*-(3-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (s, 6H), 4.08 (s, 3H), 9.90 (s, 1H).

Example 30

2-Methoxy-4-methylamino-benzoic acid methyl ester

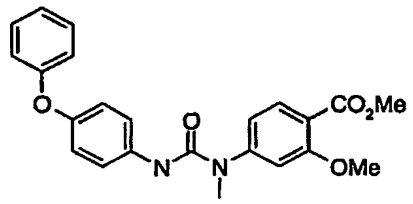


A solution of sodium methoxide (0.745g, 13.8 mmol), paraformaldehyde (0.124g, 4.14 mmol) and methyl 4-amino-2-methoxybenzoate (050g, 2.76 mmol) in methanol (40μL) was stirred overnight at 40°C before sodium borohydride (0.229g, 6.07 mmol) was added at room temperature. The resulting mixture was heated at 50°C for 8 hours. Methanol was removed *in vacuo*. The residue was partitioned between saturated aqueous NaHCO3 and dichloromethane. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3x20 mL). The combined organic phases were dried over

$MgSO_4$, filtered and evaporated *in vacuo* to give a crude solid which was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 95/4.5/0.5) to give the title compound as a white solid (0.278g, 1.43 mmol, 52%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.88 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.30 (bs, 1H), 6.07 (s, 1H), 6.14 (d, 1H), 7.76 (d, 1H)

Example 31

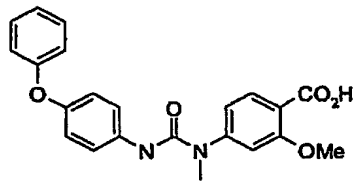
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid methyl ester



The title compound **Ex 31** was obtained by carrying out the same procedure as in Example 8, using **Ex 30** and commercially available 4-phenoxyphenylisocyanate. ^1H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.91 (s, 6H), 6.35 (s, 1H), 6.93-7.26 (m, 11H), 7.88 (d, 1H)

Example 32

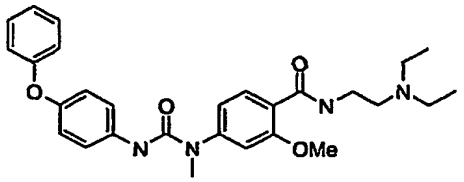
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid



A solution of **Ex 31** (0.38g, 0.93 mmol) and lithium hydroxide (0.034g, 1.4mmol) in a THF/water mixture (2/1, 6μL) was stirred at 30°C for 3 days. After removal of the solvent *in vacuo*, the residue was diluted with water and washed with dichloromethane. The aqueous phase was then saturated with solid sodium chloride and acidified to pH = 1 with a 6N aq. HCl solution. The aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **Ex 32** as a white solid (0.249g, 0.63mmol, 68%). ^1H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H), 4.09 (s, 3H), 6.52 (s, 1H), 6.93-7.33 (m, 11H), 8.20 (d, 1H)

Example 33

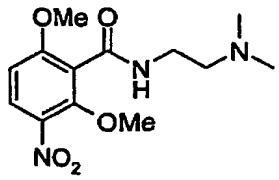
N-(2-Diethylamino-ethyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide



A solution of compound **Ex 32** (0.02 g, 0.051 mmol), EDAC (0.0146 g, 0.076 mmol) and HOBt (0.0089 g, 0.066 mmol) in dichloromethane (3 μL) was stirred at RT for 5 minutes before *N,N*-diethylethylenediamine (0.0086 μL) was added. The resulting reaction mixture was stirred at RT overnight, washed with saturated aq. NaHCO3 solution (3x), brine, dried over MgSO4 and concentrated *in vacuo*. The crude was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 90/9/1) to give the title compound as a colourless oil which crystallised upon standing (0.025 g, 0.051 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 6H), 2.58 (q, 4H), 2.66 (t, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.97 (s, 3H), 6.36 (s, 1H), 6.91-7.32 (m, 11H), 8.29 (d, 1H), 8.35 (bs, 1H)

Example 34

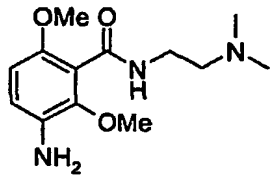
N-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-nitro-benzamide



A flask was charged with 2,6-dimethoxy-3-nitrobenzoic acid (1 g, 4.4 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.27 g, 6.6 mmol), hydroxybenzotriazole (772 mg, 5.72 mmol) and N,N-dimethylethylene diamine (0.48 μL, 4.4 mmol). Dichloromethane (50 μL) was added and the suspension was stirred under air for 16 h. The now clear reaction mixture was washed consecutively with water (2 x 20 μL) and brine (1 x 20 μL). The organic solution was then briefly dried over sodium sulfate before being filtered and reduced *in vacuo* to give *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (2H, d), 6.77-6.72 (2H, d), 6.50-6.30 (1H, br s, NH), 3.97 (3H, s, MeO), 3.92 (3H, s, MeO), 3.60-3.45 (2H, m), 2.55-2.45 (2H, m), 2.25 (6H, s, Me_2N).

Example 35

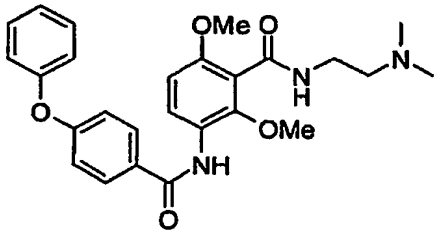
3-Amino-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide



To a solution of *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide (1.31 g, 4.4 mmol) in dry methanol (50 μL) was added 10% palladium on carbon (50 mg). The reaction vessel was sealed and the atmosphere exchanged with nitrogen. The solution was then vigorously stirred and the atmosphere exchanged with hydrogen via a double balloon. Stirring continued for 16 h before the ballon was removed and the reaction mixture was filtered through a plug of celite (approx. 10 g). The residues were washed with excess methanol (approx. 100 μL) and the combined filtrates were reduced *in vacuo* returning a crude product which was chromatographed (Al_2O_3, dichloromethane-/methanol/triethylamine, 90:9:1) to give *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99-7.91 (1H, m), 6.72-6.67 (1H, m), 3.88 (3H, s, MeO), 3.85 (3H, s, MeO), 3.72-3.67 (2H, m), 3.13-3.05 (2H, m), 2.72 (6H, s, Me_2N).

Example 36

***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(4-phenoxy-benzoylamino)-benzamide**

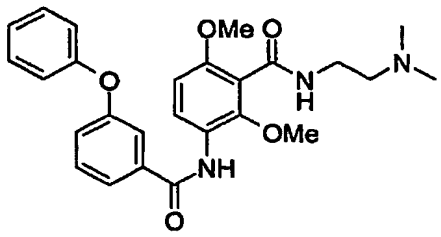


A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (8 mg, 32 μmol), hydroxybenzotriazole (5.6 mg, 46 μmol), *N,N*-dimethylaminopyridine (1 crystal) and 4-phenoxybenzoic acid (6.8 mg, 32 μmol). Dichloromethane (10 μL) was added and the solution was stirred under air before PS-DCC (60 mg, approx. 64 μmol) was added. Stirring continued for 72 h before PS-trisamine (200 mg) was added and the resulting suspension stirred for 3 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the

combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title product. ^1H NMR (300 MHz, $CDCl_3$): δ 8.45-8.38 (1H, d), 8.40-8.30 (1H, br s, NH), 7.60-7.30 (5H, m), 7.22-7.12 (2H, m), 7.08-7.00 (1H, d), 6.74-6.55 (1H, d), 6.52-6.48 (2H, m, Ar-H + NH), 3.89 (3H, MeO), 3.83 (3H, MeO), 3.58-3.52 (2H, m), 2.54-2.48 (2H, m), 2.26 (6H, s, Me_2N).

Example 37

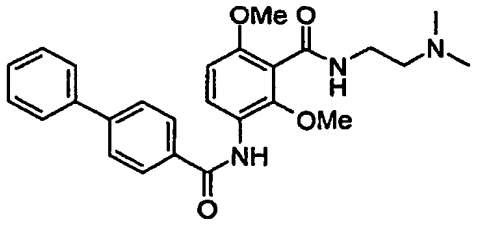
***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(3-phenoxy-benzoylamino)-benzamide**



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and 3-phenoxybenzoic acid (79 mg, 0.40 mmol). Dichloromethane (8 μL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42-8-38 (1H, d), 8.35-8.28 (1H, br s, NH), 7.48-7.35 (5H, m), 7.25-7.10 (2H, m), 7.08-7.10 (2H, d), 6.75-7.69 (1H, d), 6.68-6.48 (1H, br s, NH), 3.89 (3H, s, MeO), 3.83 (3H, s, MeO), 3.58-3.52 (2H, m), 2.53-2.49 (2H, m), 2.25 (6H, s, Me_2N).

Example 38

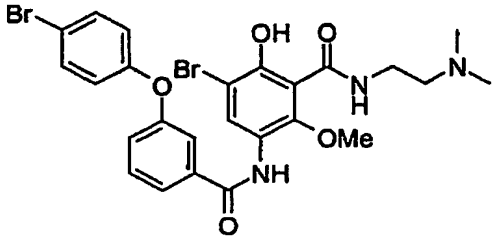
Biphenyl-4-carboxylic acid [3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and biphenylacetic acid (79 mg, 0.40 mmol). Dichloromethane (8 μL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55-8.45 (1H, d), 8.45-8.35 (1H, br s, NH), 7.97-7.95 (2H, d), 7.80-7.70 (2H, d), 7.70-7.60 (2H, d), 7.60-7.40 (3H, m), 6.76-6.73 (1H, d), 6.60-6.50 (1H, br s, NH), 3.67 (3H, s, MeO), 3.86 (3H, s, MeO), 3.61-3.55 (2H, m), 256-2.52 (2H, m), 2.28 (6H, s, Me_2N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 165.1, 153.6, 147.8, 140.3, 134.0, 129.4, 128.5, 127.9, 127.6, 125.5, 122.4, 120.4, 120.4, 107.3, 62.7, 58.0, 56.6, 46.3, 45.5, 37.7.

Example 39

3-Bromo-5-[3-(4-bromo-phenoxy)-benzoylamino]-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide

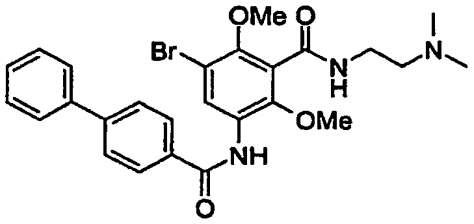


To a solution of **Ex 37** (120 mg, 0.26 mmol) in dichloromethane (10 μL) with acetic acid (1 drop) was added bromine (27 μL, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 μL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 μL) and brine (10 μL) before being dried over sodium sulphate, filtered and reduced *in*

vacuo. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 9.10-9.00 (1H, br app s, NH), 8.88 (1H, s), 8.60-8.50 (1H, br s, NH), 7.64-7.60 (1H, dt), 7.57-7.56 (1H, t), 7.53-7.45 (3H, m), 7.21-7.18 (1H, dd), 6.98-6.93 (2H, d), 3.89 (3H, s, MeO), 3.58-3.53 (2H, q, CH_2NH), 2.59-2.57 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 40

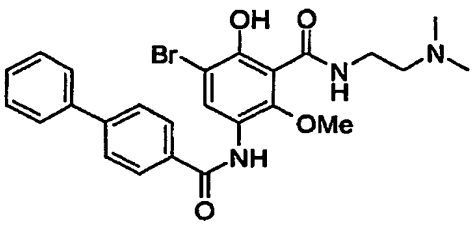
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



To a solution of **Ex 38** (120 mg, 0.26 mmol) in dichloromethane (10 μL) with acetic acid (1 drop) was added bromine (27 μL, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 μL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 μL) and brine (10 μL) before being dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (1H, s), 8.50-8.60 (1H, br s, NH), 7.98-7.93 (2H, d), 7.77-7.72 (2H, d), 7.67-7.62 (2H, m), 7.58-7.35 (3H, m), 6.92-6.80 (1H, br s, NH), 3.96 (3H, s, MeO), 3.89 (3H, s, MeO), 3.64-3.59 (2H, q, CH_2NH), 2.65-2.58 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 41

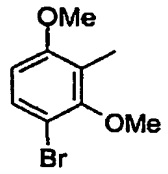
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-4-hydroxy-2-methoxy-phenyl]-amide



From the above reaction a second product was isolated and identified as **Ex 41**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.07-9.04 (1H, br s, NH), 8.96 (1H, s), 8.75-8.65 (1H, br s, NH), 8.02-7.99 (2H, d), 7.76-7.73 (2H, d), 7.68-7.65 (2H, d), 7.60-7.35 (3H, m), 3.90 (3H, s, MeO), 3.59-3.54 (2H, q, CH_2NH), 2.58-2.54 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 42

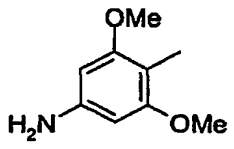
1-Bromo-2,4-dimethoxy-3-methyl-benzene



To a solution of 2,6-dimethoxytoluene (5 g, 33 mmol) in dichloromethane (100 μL) and acetic acid (1 drop) held at 0 °C was added bromine (1.67 μL, 33 mmol) dropwise. The pale brown solution was stirred for a further 5 h before being washed with a saturated solution of sodium thiosulfate (20 μL), sodium bicarbonate (20 μL), water (20 μL) and brine (20 μL). The organic solution was then dried over sodium thiosulfate, filtered and evaporated *in vacuo* to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.32 (1H, d), 6.56-6.53 (1H, d), 3.82 (3H, s, MeO), 3.81 (3H, s, MeO), 2.22 (3H, s, CH_3).

Example 43

3,5-Dimethoxy-4-methyl-phenylamine

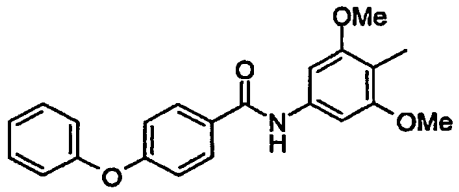


To a freshly prepared suspension of potassium amide (from potassium 12.87 g, 330 mmol) in liquid ammonia (300 μL) held at -78°C was added *example 9* (7.6 g, 33 mmol) dropwise over twenty minutes. The resulting suspension was stirred for a further 3 h and then excess potassium amide was quenched carefully with solid ammonium chloride (10 g) added portionwise over thirty minutes. Toluene (200 μL) was added and the liquid ammonia allowed to evaporate. The organic solution was then washed with water (3 x 100 μL) before being shaken with hydrochloric acid (6 N, 200 μL). The nascent precipitate was then collected by filtration and further washed with water (100 μL). The

residue was stirred with sodium hydroxide (10 N, 100 µL) for 1 h to form the free aniline, which was collected by filtration. The residues were washed with water (3 x 20 µL) and dried *in vacuo* to give the title compound.

Example 44

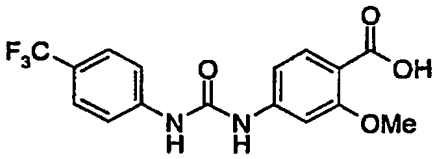
***N*-(3,5-Dimethoxy-4-methyl-phenyl)-4-phenoxy-benzamide**



A flask was charged with **Ex 43** (334 mg, 2 mmol), 4-phenoxybenzoic acid (471 mg, 2.2 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (573 m g, 3 mmol) and hydroxybenzotriazole (351 mg, 2.6 mmol). Dichloromethane (20 µL) was added and the suspension was stirred for 100 h. The now clear solution was washed with hydrochloric acid (1 N, 20 µL), sodium bicarbonate (20) and water (20 µL). The organic solution was dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 98:1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (2H, d), 7.75 (1H, s), 7.50-7.40 (2H, m), 7.25-7.15 (1H, m), 7.12-7.05 (4H, m), 6.93 (2H, s), 5.95 (1H, s), 3.85 (6H, s, MeO), 2.09 (3H, s, CH_3).

Example 45

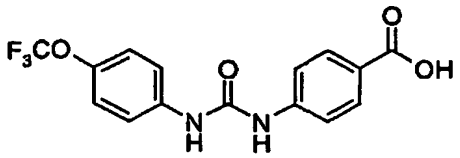
2-Methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzoic acid



To a solution of 4-amino-2-methoxybenzoic acid (3.4 g, 20.3 mmol) in dry dichloromethane (300 mL) under inert atmosphere was 4-trifluoromethylphenyl isocyanate (5.0 g, 26.7 mmol) added drop wise. The reaction was stirred over night at room temperature and a precipitate was formed during the reaction. The precipitate was filtered and washed with dichloromethane and gave 5.7 g (79 %) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 3.8 (s, 3H), 6.9 (dd, 1H), 7.4 (d, 1H), 7.4-7.7 (m, 5H), 9.2 (d, 2H), 12.2 (s, 1H). LCMS(an20n15); RT = 8.306 min, 352.9 m/z

Example 46

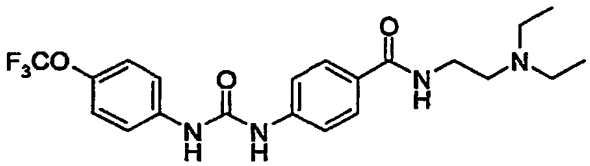
4-[3-(4-Trifluoromethoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described above was the title product synthesised from 4-amino-benzoic acid (1.2 g, 7.6 mmol) and 4-trifluoromethoxyphenyl isocyanate (2.0 g, 9.8 mmol) giving 2.7 g (quant.) of the product.
LCMS(an20n15); RT = 7.503 min, 338.8 m/z.

Example 47

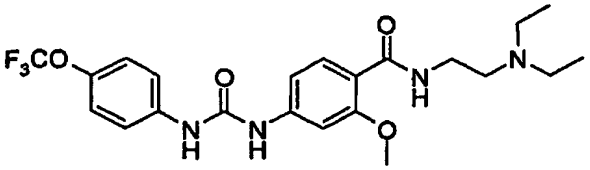
***N*-(2-Diethylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of procainamide (26 mg, 0.112 mmol) in dichloromethane (1.5 mL) under inert atmosphere were triethylamine (31 μL) and 4-trifluoromethoxyphenyl isocyanate (30 μL, 0.145 mmol) added. The reaction was stirred for three days. PS-Trisamine (0.16 g, 3.58 mmol/g, 0.56 mmol) was added and the reaction was stirrede for two more days. The resin was filtered off and the reaction mixture was concentrated *in vacuo*. The crude product was purified by acidic ion exchange chromatography (SCX-colon) giving 29 mg (59%) of the title product. LCMS (an20p10): RT = 5.52 min, (M-1) = 439.0 m/z.

Example 48

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

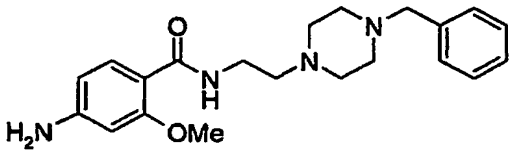


To a solution of 2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoic acid (example 153) (50 mg, 0.135 mmol) in dichloromethane (3.5 mL) and dimethylformamide (0.35 mL) was added to polystyrene-DCC (0.5 g, 1.27 mmol/g, 0.64 mmol). Thereafter were HOBT (40 mg, 0.30 mol) and N^1,N^1-diethyl-ethyldiamine (18 μL, 16.5 mg 0.14 mmol) added and

the reaction was stirred over night. The resin was filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 12 mg (18%) of the title product. LCMS (an20p10): RT = 4.95 min, (M+1) = 469.0 m/z.

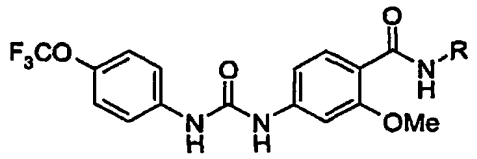
Example 49

4-Amino-*N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide

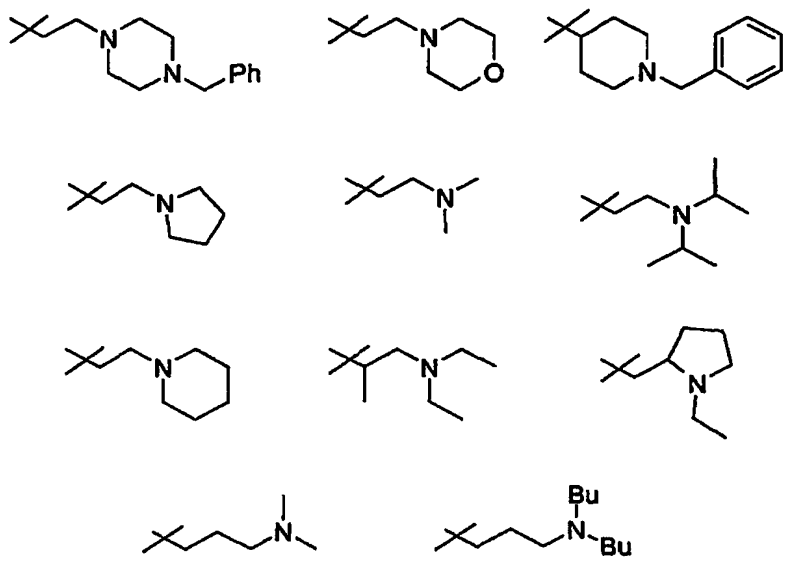


To a solution of 2-(4-Benzyl-piperazin-1-yl)-ethylamine (10 g, 45 mmol) in dry dichloromethane (500 mL) were EDC (11.3 g, 58 mmol), 2-methoxy-4-nitro-benzoic acid (11 g, 55 mmol) and HOBt (7.6 g, 56 mmol) added. The reaction mixture was left stirring at room temperature for four days. To the reaction was dichloromethane (3 L) added which was washed with Na2CO3 (sat.) (0.5 L). and the water phase was extracted with dichloromethane (3 L). The combined organic phases were dried (MgSO4), and concentrated *in vacuo*. The crude product (30 g) was chromatographed (silica, EtOAc/Heptane/triethylamine, 60:33:7) giving 17 g of 4-nitro-*N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide (96 %). The product (4.3 g, 10.7 mmol) was dissolved in methanol (430 mL) and 5 % Pt/C (430 mg) was added under a nitrogen flow. The mixture was stirred in an H_2 atmosphere over night. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo* giving 3.5 g (89%) of the title product. LCMS (an20p15); RT = 2.73 min, (M+1) = 369.

According to the procedure outlined in example 48 were the following compounds prepared utilizing **Ex 153** and the corresponding primary amines to the R-group, if not noted otherwise;



R =



Example 50

_N_-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

To a solution of 4-Amino-_N_-[2-(4-benzyl-piperazin-1-yl)-ethyl]-2-methoxy-benzamide (example 49) (60 mg, 0.163 mmol) in dichloromethane (2 mL) was 4-trifluoromethoxyphenyl isocyanate (45 mg, 0.22 mmol) added and the reaction was stirred under inert atmosphere over weekend. PS-Trisamine (100 mg, 3.58 mol/g) was added and the reaction mixture was continuously stirred over night. The resin was filtered off and washed twice with dichloromethane. The solvent was removed *in vacuo*. The crude product was purified through acidic ion exchange chromatography (SCX-colon) and as eluent was dichloromethane followed with methanol used. From the methanol was isolated 27 mg of the title product. LCMS(an20p15); RT = 6.61 min, (M+1) = 572.1

Example 51

2-Methoxy-_N_-(2-morpholin-4-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 153 and 3-Morpholin-4-yl-ethylamine were coupled giving 11 mg (16%) of the title product. LCMS(an20p15); RT = 5.99 min, (M+1) = 483.0.

Example 52

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and 1-Benzyl-piperidin-4-ylamine were coupled giving 11 mg (46%) of the title product. LCMS(an20p15); RT = 5.90 min, (M+1) = 543.0.

Example 53

2-Methoxy-*N*-(2-pyrrolidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 153 and 2-Pyrrolidin-1-yl-ethylamine were coupled giving 12 mg (19%) of the title product. LCMS(an20p15); RT = 8.22 min, (M+1) = 467.0

Example 54

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and N^1,N^1-Dimethyl-ethane-1,2-diamine were coupled giving 7.8 mg (13%) of the title product. LCMS(an20p15); RT = 5.91 min, (M+1) = 440.9

Example 55

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and N^1,N^1-Diisopropyl-ethane-1,2-diamine were coupled giving 17 mg (26%) of the title product. LCMS(an20p15); RT = 7.92 min, (M+1) = 497.0

Example 56

2-Methoxy-*N*-(2-piperidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 153 and 2-Piperidin-1-yl-ethylamine N^1,N^1-Diethyl-propane-1,2-diamine were coupled giving 12 mg (18%) of the title product. LCMS(an20p15); RT = 8.53 min, (M+1) = 481.0

Example 57

***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and N^1,N^1-Diethyl-propane-1,2-diamine were coupled giving 9.2 mg (14%) of the title product. LCMS(an20p15); RT = 6.17 min, (M+1) = 483.0

Example 58

***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and C-(1-Ethyl-pyrrolidin-2-yl)-methylamine were coupled giving 12 mg (19%) of the title product. LCMS(an20p15); RT = 7.52 min, (M+1) = 481.0

Example 59

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and N^1,N^1-Dimethyl-propane-1,3-diamine were coupled giving 12 mg (20%) of the title product. LCMS(an20p15); RT = 5.93 min, (M+1) = 455.0

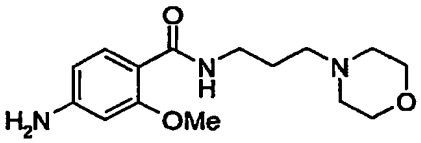
Example 60

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 153 and N^1,N^1-Dibutyl-propane-1,3-diamine were coupled giving 14 mg (20%) of the title product. LCMS(an20p15); RT = 7.25 min, (M+1) = 539.1

Example 61

4-Amino-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

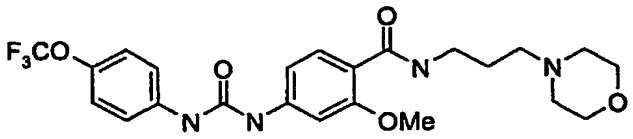


2-methoxy-4-nitro-benzoic acid (3.0 g, 15.5 mmol) was dissolved in THF(180 ml) and the mixture was heated to reflux (70 °C). Carbonyl diimidazol (3.7 g, 22.8 mmol) was added in 3 portions with 20 minutes intervals – with continued refluxing. After the last addition reaction is allowed to reflux for another 1 h. The reaction mixture was cooled to room temperature followed by addition of 3-morpholin-4-yl-propylamine (4.4 g, 30.4 mmol) and the reaction was left overnight. The solvent was removed *in vacuo* and to the crude product was added a mixture of 200 ml EtOAc and 200 ml of water. The organic phase is washed with 2*200 ml water and 1*200 ml of brine. The combined organic phases was dried over $MgSO_4$ and concentrated giving a clear oil. Crystallisation can be obtained by adding diethylether followed by evaporation. The product (7.6 g, 23 mmol) was dissolved in methanol (120 ml) and 10 % Pd/C (40 mg) was added. A pressure of hydrogen atmosphere was applied and the reaction was left over night. Filtration through a plug of celite gave 7.36 g of the title product (94 % over all yield).

^{1}H-NMR (300 MHz, CD_3Cl): δ 1H, 7.79 (s, 1H), 4.03 (s, 2H), 3.90 (s, 3H).

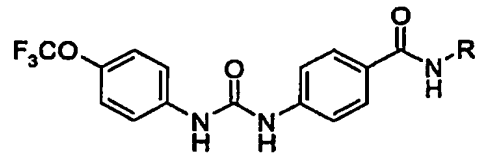
Example 62

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

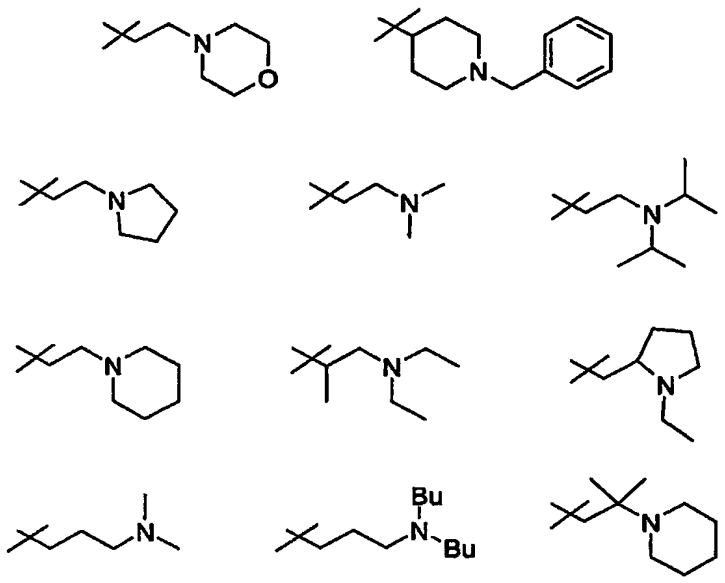


To a solution of 4-Amino-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide (20 mg, 0.068 mmol) (example 61) in dichloromethane (1 mL) was 4-trifluoromethoxyphenyl isocyanate (19 □L , 0.136 mmol) added and the reaction was stirred under inert atmosphere for three days. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol, 92:8) giving 3.4 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.89 (s, 3H), 8.04 (br t, 1H), 9.09 (s, 1H), 9.12 (s, 1H). LCMS(an10p15): found (M+1) = 497.

According to the procedure outlined in example 48 were the following compounds prepared utilizing **Ex 46** and the corresponding primary amines to the R-group, if not noted otherwise;



R =



Example 63

***N*-(2-Morpholin-4-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and 3-Morpholin-4-yl-ethylamine were coupled giving 18 mg (27%) of the title product. LCMS(an20p15); RT = 5.77 min, (M+1) = 452.9

Example 64

***N*-(1-Benzyl-piperidin-4-yl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and 1-benzyl-piperidin-4-ylamine were coupled giving 20 mg (28%) of the title product. LCMS(an20p15); RT = 6.28 min, (M+1) = 513.0

Example 65

***N*-(2-Pyrrolidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and 2-pyrrolidin-1-yl-ethylamine were coupled giving 15 mg (24%) of the title product. LCMS(an20p15); RT = 5.87 min, (M+1) = 437.0

Example 66

***N*-(2-Dimethylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and N^1,N^1-dimethyl-ethane-1,2-diamine were coupled giving 5.7 mg (10%) of the title product. LCMS(an20p15); RT = 5.65 min, (M+1) = 410.9

Example 67

***N*-(2-Diisopropylamino-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and N^1,N^1-diisopropyl-ethane-1,2-diamine were coupled giving 14 mg (21%) of the title product.

Example 68

***N*-(2-Piperidin-1-yl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and 2-piperidin-1-yl-ethylamine were coupled giving 17 mg (26%) of the title product.

Example 69

***N*-(2-Diethylamino-1-methyl-ethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and N^1,N^1-diethyl-propane-1,2-diamine were coupled giving 16 mg (25%) of the title product. LCMS(an20p15); RT = 5.88 min, (M+1) = 453.0

Example 70

***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and C-(1-ethyl-pyrrolidine-2-yl-methylamine were coupled giving 19 mg (30%) of the title product. LCMS(an20p15); RT = 6.07 min, (M+1) = 451.0

Example 71

***N*-(3-Dimethylamino-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**

Ex 46 and N^1,N^1-Dimethyl-propane-1,3-diamine were coupled giving 11 mg (18%) of the title product. LCMS(an20p15); RT = 5.72 min, (M+1) = 425.0

Example 72

N-(3-Dibutylamino-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 46 and N^1,N^1-Dibutyl-propane-1,3-diamine were coupled giving 15 mg (21%) of the title product. LCMS(an20p15); RT = 7.04 min, (M+1) = 509.1

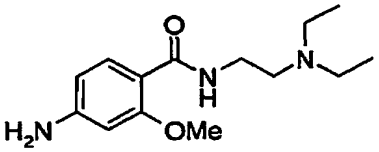
Example 73

N-(2-Methyl-2-piperidin-1-yl-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 46 and 2-Methyl-2-piperidin-1-yl-propylamine were coupled giving 18 mg 26(%) of the title product. LCMS(an20p15); RT = 6.20 min, (M+1) = 479.0

Example 74

4-Amino-N-(2-diethylamino-ethyl)-2-methoxy-benzamide

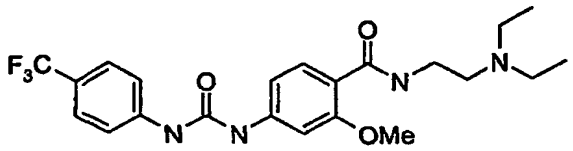


A solution of 2-Methoxy-4-nitrobenzoic acid (1.5 g, 7.6 mmol) in dry dichloromethane (15 mL) was placed on an ice bath whereupon oxalyl chloride (0.6 mL, 6.8 mmol) followed by *N,N*-dimethylformamide (2 μL) were added under inert atmosphere. The mixture was stirred for 30 min at 0 °C followed by 1h in room temperature. Triethylamine (2.1 mL, 15 mmol) and N,N-diethylethylenediamine (1.1 mL, 7.6 mmol) were added and a precipitation was formed. The reaction mixture was stirred for 48h. To the reaction mixture was added EtOAc (60 mL) and the organic layer was washed with Na_2CO_3 (sat.), dried ($MgSO_4$), and concentrated *in vacuo*. The reaction was giving 2.0 g of *N*-(2-diethylamino-ethyl)-2-methoxy-4-nitro-benzamide (99 %). ^{1}H NMR (300 MHz, CD_3Cl): δ 1.06 (t, 6H), 4.07 (s, 3H).

The product (2.0 g, 6.8 mmol) was dissolved in ethanol (20 mL) and 10 % Pd/C (50 mg) was added and thereafter was the flask evacuated and filled with nitrogen. The mixture was stirred in an H_2 atmosphere 48h. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo*. The crude product was chromatographed (silica, dichloromethane/ethanol/ ammoniak, 100:15:1.5) giving 1.0 g (57%) of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (t, 6H), 2.53-2.65 (m, 6H).

Example 75

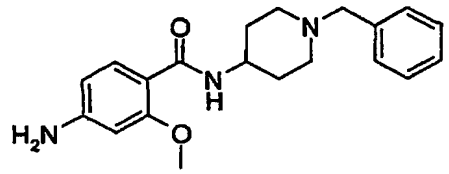
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide



To a solution of *N*-(2-Diethylamino-ethyl)-2-methoxy-4-amino-benzamide (20 mg, 0.075 mmol) (example 74) in dichloromethane (1 mL) was trifluorophenylisocyanate (28 mg, 0.15 mmol) added and the reaction was stirred under inert atmosphere for four days. A white precipitate had been formed. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol/ammoniak, 200:10:1) giving 11 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (t, 6H), 2.56 (q, 4H), 2.65 (t, 2H), 3.54 (q, 2H), 3.94 (s,3H), 6.48 (dd, 1H), 7.56 (q, 4H), 7.83 (d, 1H), 7.92 (d, 1H), 8.74 (t, 1H), 8.91 (s, 1H), 8.93 (s, 1H).

Example 76

4-Amino-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide



The title compound was prepared according to the example described in example 74 giving after the two reaction steps and the purification procedure 0.6 g (33%) of the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.52 (s, 2H), 4.02-4.11 (m, 1H), 3.86 (s, 3H).

A general method for preparing unsymmetrical amines:

Example 77

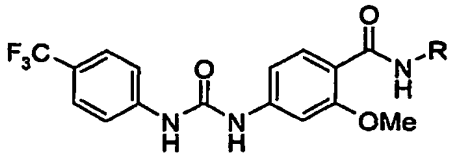
***N*^{1}-methyl,*N*^{1}-ethyl- ethyldiamine hydro chloride**

To a suspension of bromoethylphtalimide (8.9 g, 35 mmol) in dry xylene (18 mL) was *N*-ethylmethylamine (6.25 mL, 73 mmol) added and the reaction was stirred over night at 150°C. The reaction was allowed to reach room temperature before it was made basic with 2 M Na_2CO_3-solution (pH = 9). Thereafter was the reaction extracted with EtOAc (3 x 70 mL) and the combined organic phases dried ($MgSO_4$) and evaporated giving a brownish oil. Water (2 mL) and 12 N HCl (12 mL) were added and the solution was heated for 6h at 130°C when a precipitation was formed. The precipitate was filtered off and washed with cold water and the water phase was evaporated giving 4.8 g (78%) of the title product.

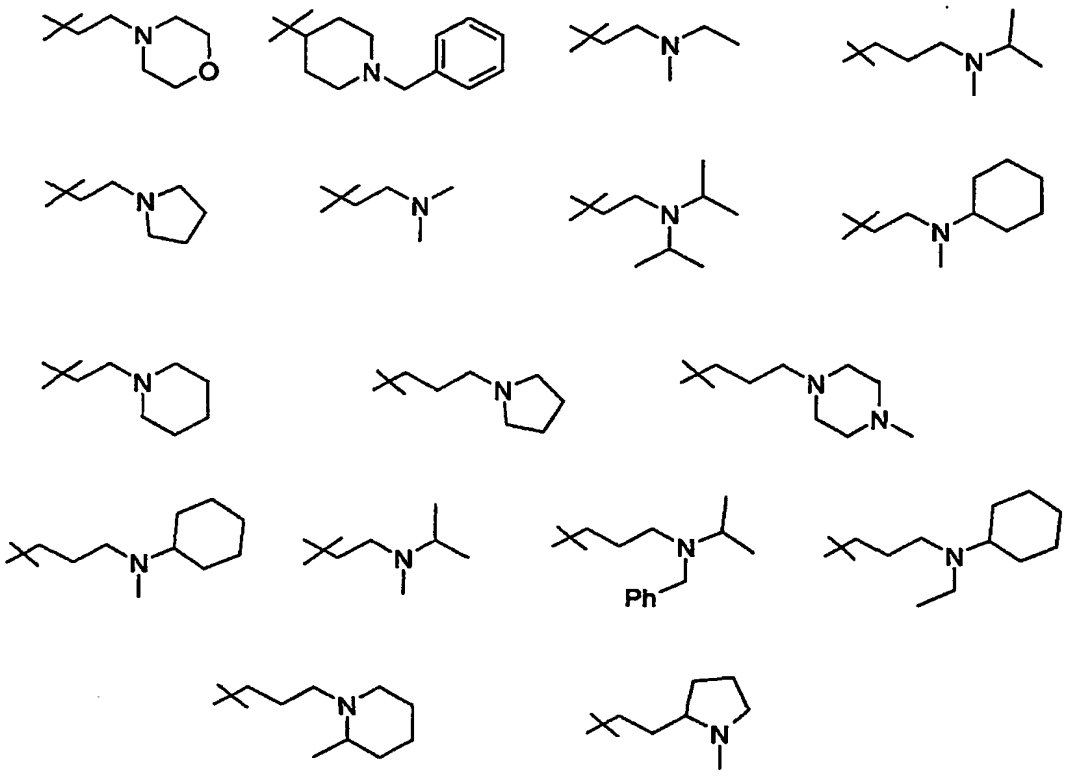
According to the general procedures described hereby, the following compounds were prepared:

Method A: To a solution of Ex. 45 (30 mg, 0.085 mmol) in dichloromethane (0.25 mL) and dimethylformamide (0.25 mL) was HOBT (12 mg, 0.085 mmol) added and the solution was cooled to 0°C whereupon EDAC (16 mg, 0.085 mmol) was added. The reaction was left at 0°C for 20 min before the amine (1-1.5 equiv.) and diisopropylethylamine (1-3 equiv.) were added and the stirring continued at room temperature for one day or more. EtOAc was added to the reaction mixture and the organic phase was washed with $NaHCO_3$ (sat). The aqueous phase was extracted with EtOAc and the combined organic phases was dried ($MgSO_4$) and concentrated giving the crude product.

Method B: To a solution of Ex. 45 (70 mg, 0.20 mmol) in dichloromethane (3.5 mL) and *N,N*-dimethylformamide (0.35 mL) were PS-DDC (0.5 g, 1.27 mmol/g), HOBT (40 mg, 0.29 mmol) and the amine 1 equiv.) added and the mixture was stirred over night. The reaction mixture was filtered off and washed with dichloromethane, and concentrated *in vacuo*. The crude product was purified by acidic ion exchange chromatography (SCX-colon) the product.



R =



Example 78

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 35 mg (53%) of the product. LCMS (an20p15): RT = 5.72 min, (M+1) = 467.

Example 79

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.49 min, (M+1) = 527. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.48 (s, 2H), 3.93 (s, 3H), 3.93-4.05 (m, 1H), 8.12 (s, 1H), 8.15 (s, 1H).

Example 80

***N*-[2-(Ethyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.49 min, (M+1) = 439. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.08 (t, H), 2.27 (s, 3H), 3.95 (s, 3H), 9.01 (s, 1H), 9.03 (1H).

Example 81

***N*-[3-(Isopropyl-methyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 0.98 (d, 6H), 2.20 (s, 3H), 3.91 (s, 3H), 8.66 (s, 1H), 8.90 (s, 1H).

Example 82

2-Methoxy-*N*-(2-pyrrolidin-1-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 29 mg (46%) of the product. LCMS (an20p15): RT = 5.79 min, (M+1) = 451.

Example 83

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method B was the title compound synthesised giving 13 mg (23%) of the product. LCMS (an20p15): RT = 5.66 min, (M+1) = 425.

Example 84

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method B was the title compound synthesised giving 18 mg (27%) of the product. LCMS (an20p15): RT = 6.32 min, (M+1) = 481.0 m/z.

Example 85

***N*-[2-(Cyclohexyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.65 min, (M+1) = 493. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.63 (d, 1H), 2.31 (s, 3H), 3.91 (s, 3H), 9.08 (s, 2H).

Example 86

2-Methoxy-*N*-(2-piperidin-1-yl-ethyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method B was the title compound synthesised giving 14 mg (22%) of the product. LCMS (an20p15): RT = 5.99 min, (M+1) = 465.

Example 87

2-Methoxy-*N*-(3-pyrrolidin-1-yl-propyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.93 min, (M+1) = 465. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.90 (s, 3H), 9.08 (s, 1H), 9.14 (s, 1H).

Example 88

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.05 min, (M+1) = 494. ^{1}H NMR (300 MHz, CD_3Cl): δ 2.28 (s, 3H), 3.94 (s, 3H), 9.03 (s, 1H), 9.07 (s, 1H).

Example 89

***N*-[3-(Cyclohexyl-methyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.61 (d, 1H), 2.26 (s, 3H), 3.90 (s, 3H), 9.07 (s, 1H), 9.13 (s, 1H).

Example 90

***N*-[2-(Isopropyl-methyl-amino)-ethyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.12 min, (M+1) = 453. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.05 (d, 6H), 2.27 (s, 3H), 2.89-2.98 (m, 1H), 3.92 (s, H), 9.07 (s, 1H).

Example 91

***N*-[3-(Benzyl-isopropyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.27 min, (M+1) = 543. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.01 (d, 6H), 3.55 (s, 2H), 3.82 (s, 3H), 9.09 (s, 1H), 9.15 (s, 1H).

Example 92

***N*-[3-(Cyclohexyl-ethyl-amino)-propyl]-2-methoxy-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide**

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.13 min, (M+1) = 521. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.00 (t, 3H), 1.61 (d, 1H), 3.89 (s, 3H), 9.10 (s, 1H), 9.16 (s, 1H).

Example 93

2-Methoxy-*N*-[3-(2-methyl-piperidin-1-yl)-propyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 6.26 min, (M+1) = 493. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.03 (d, 3H), 3.92 (s, 3H), 9.03 (s, 1H), 9.09 (s, 1H).

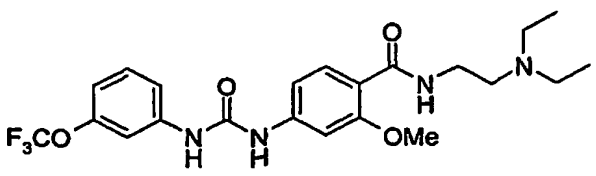
Example 94

2-Methoxy-*N*-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

According to method A was the title compound synthesised giving the product. LCMS (an20p15): RT = 5.76 min, (M+1) = 465. ^{1}H NMR (300 MHz, CD_3Cl): δ 2.30 (s, 3H), 3.94 (s, 3H), 9.00 (s, 1H), 9.02 (s, 1H).

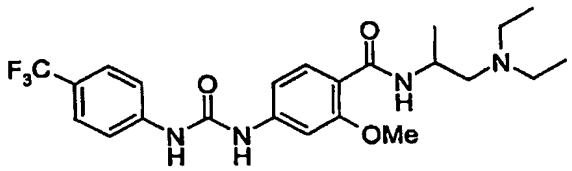
Example 95

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide**



Example 96

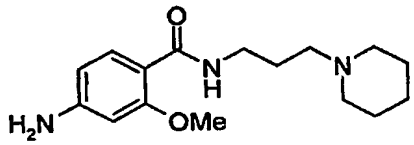
***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide**



To a solution of 4-amino-*N*-(2-diethylamino-1-methyl-ethyl)-2-methoxy-benzamide (56 mg, 0.2 mmol) (synthesised using the same method as for example 74) in dry dichloromethane (5mL) was 4-trifluorotosyl isocyanate (35 □L, 0.25 mmol) added and the reaction was stirred under inert atmosphere for four days. The solvent was removed *in vacuo*. The crude product was chromatographed (Al_2O_3, CH_2Cl_2/methanol/ammoniak, 10:0.25+0.5%) giving 27 mg of the title product (29 %).

Example 97

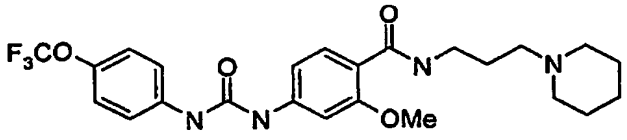
4-Amino-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide



To a refluxing solution of 2-methoxy-4-nitro-benzoic acid (5.6 g, 29 mmol) in dry THF (mL) was carbonyldiimidazol (3 x 2.3 g, 42 mmol) added in three portions with 15 min in between. After 20 minutes continuous refluxing the reaction was cooled to room temperature and 3-amino-propyl-piperidine (4.5 g, 32 mmol) was added. The reaction mixture was left stirring over night. Water and EtOAc was added and the organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol/ammoniak, 9:1 + 1%) giving 6.8 g of 2-methoxy-4-nitro-N-(3-piperidin-1-yl-propyl) benzamide (74 %). The product was dissolved in ethanol (250 mL) and 10 % Pd/C (200 mg) was added under a nitrogen flow. A balloon containing H_2 was collected to the flask and the reaction mixture was stirred for 2h. The catalyst was filtered off using a pad of celite and the remaining solution was concentrated *in vacuo* giving 4.9 g (80 %) of the title product.

Example 98

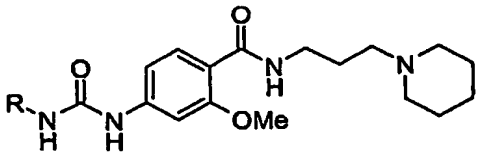
2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzamide



To a solution of example 97 (58 mg, 0.2 mmol) in dichloromethane was 4-trifluoromethoxyphenyl isocyanate (35 μL, 0.25 mmol) added and the reaction was stirred over night in inert atmosphere. The solvent was removed *in vacuo*. The crude product was chromatographed (Al_2O_3, CH_2Cl_2/methanol/ammoniak, 10:0.25+0.5%) giving 20 mg of the title product (20 %).

According to the procedure described in example 98 (from anilines and isocyanates) or according to the general method described below (from anilines and carboxylic acid) were the following compounds prepared:

General method for preparing ureas from anilines and carboxylic acids:
To a solution of the carboxylic acid (0.25 mmol) in dry toluene (5 mL) under inert atmosphere were diphenylphosphoryl azide (54 μL, 0.25 mmol) and triethylamine (35 μL, 0.25 mmol) and the reaction mixture was heated to reflux for 1h. 4-Amino-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide, Example 97 (44 mg, 0.15 mmol) dissolved in hot toluene (2 mL) was added and the reaction mixture was left over night in room temperature. The solvent was removed *in vacuo*. The crude product was usually purified through chromatography (silica, CH_2Cl_2/methanol/ammoniak, 10:0.25 + 0.5 %) giving the desired product.



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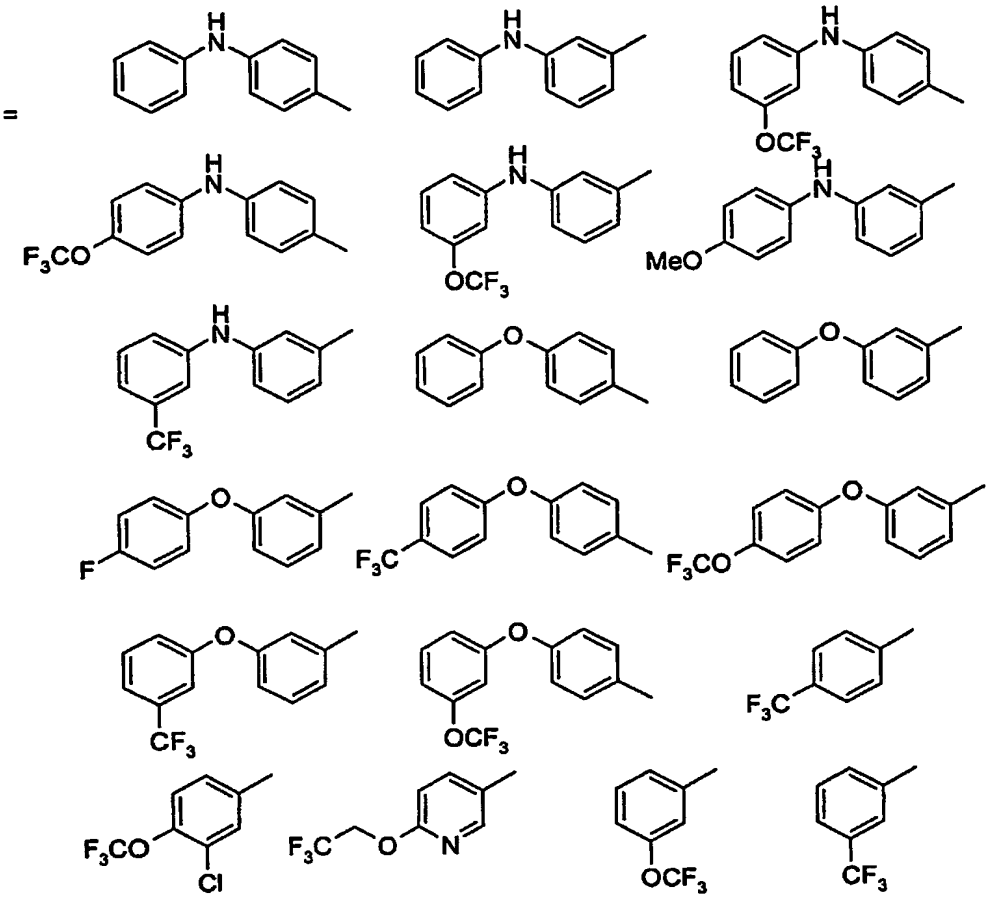


Example 99

2-Methoxy-4-[3-(4-phenylamino-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide)

Ex 97 and 4-Phenylamino-benzoic acid were coupled giving 41 mg (54%) of the title product. LCMS (an20p15): RT = 6.05 min, (M+1) =502.

Example 100

2-Methoxy-4-[3-(3-phenylamino-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 and 3-Phenylamino-benzoic acid were coupled giving 53 mg (71%) of the title product. LCMS (an20p15): RT = 5.44 min, (M+1) =502.

Example 101

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(3-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 97 and 4-(3-trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 46 mg (52%) of the title product. LCMS (an20p15): RT = 6.83 min, (M+1) = 586.

Example 102

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 97 and 4-(4-trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 67 mg (76%) of the title product. LCMS (an20p15): RT = 6.89 min, (M+1) = 586.

Example 103

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(3-trifluoromethoxy-phenylamino)-phenyl]-ureido}-benzamide

Ex 97 and 3-(3-Trifluoromethoxy-phenylamino)-benzoic acid were coupled giving 50 mg (60%) of the title product. LCMS (an20p15): RT = 6.24 min, (M+1) = 586.

Example 104

2-Methoxy-4-{3-[3-(4-methoxy-phenylamino)-phenyl]-ureido}-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 and 4-(4-Methoxy-phenylamino)-benzoic acid were coupled giving 20 mg (25%) of the title product. LCMS (an20p10): RT = 5.77 min, (M+1) = 532.

Example 105

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(4-trifluoromethyl-phenylamino)-phenyl]-ureido}-benzamide

Ex 97 and 3-(3-Trifluoromethyl-phenylamino)-benzoic acid were coupled giving 30 mg (35%) of the title product. LCMS (an20p10): RT = 6.19 min, (M+1) = 570.

Example 106

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 and 4-phenoxy-phenyl isocyanate were coupled giving 22.6 mg (23 %) of the title product. LCMS (an20p10): RT = 5.84 min, (M+1) = 503.

Example 107

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 and 3-phenoxyphenyl isocyanate were coupled giving 69 mg (68%) of the title product. LCMS (an20p15): RT = 6.55 min, (M+1) = 503.

Example 108

4-{3-[3-(4-Fluoro-phenoxy)-phenyl]-ureido}-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 and 4-(4'-fluorophenoxy)benzoic acid were coupled giving the title product. LCMS (an20p10): RT = 6.06 min, (M+1) = 521.

Example109

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethyl-phenoxy)-phenyl]-ureido}-benzamide

Ex 97 (86 mg, 0.30 mmol) and 4-(4'-trifluoromethylphenoxy)benzoic acid (160 mg, 0.57 mmol) were coupled giving 47 mg (27%) of the title product. LCMS (an20p15): RT = 6.84 min, (M+1) = 571. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.86 (t, 2H), 3.90 (s, 3H), 6.70 (d, 1H), 8.21 (t, 1H), 9.13 (s, 1H), 9.33 (s, 1H).

Example110

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-ureido}-benzamide

Ex 97 and 4-(4-trifluoromethoxy-phenoxy)-benzoic acid were coupled giving 62 mg (71%) of the title product. LCMS (an20p15): RT = 7.17 min, (M+1) = 587.

Example 111

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[3-(3-trifluoromethyl-phenoxy)-phenyl]-ureido}-benzamide

Ex 97 and 3-(3-trifluoromethyl-phenoxy)-benzoic acid were coupled giving 24 mg (28%) of the title product. LCMS (an20p10): RT = 6.41 min, (M+1) = 571.

Example 112

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[4-(3-trifluoromethoxy-phenoxy)-phenyl]-ureido}-benzamide

Ex 97 and 4-(3-Methoxy-phenoxy)-benzoic acid were coupled giving 10 mg (11%) of the title product. LCMS (an20p15): RT = 7.25 min, (M+1) = 587.

Example 113

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

Ex 97 and 4-trifluoromethylphenyl isocyanate were coupled giving 15.5 mg (16 %) of the title product. LCMS (an20p15): RT = 6.16 min, (M+1) = 479.

Example 114

4-[3-(3-Chloro-4-trifluoromethoxy-phenyl)-ureido]-2-methoxy-*N*-(3-piperidin-1-yl-propyl)-benzamide

Ex 97 (0.14 g, 0.47 mmol) and 3-chloro-4-trifluoromethoxybenzoic acid (0.20 g, 0.83 mmol) were coupled giving 38 mg (%) of the title product. LCMS (an20p15): RT = 6.54 min, (M+1) =529.

Example 115

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-{3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ureido}-benzamide

Ex 97 and 6-(2,2,2-Trifluoro-ethoxy)-nicotinic acid were coupled giving 15 mg (20%) of the title product. LCMS (an20p15): RT = 5.83 min, (M+1) = 510.

Example116

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide

Ex 97 and 3-trifluoromethoxybenzoic acid were coupled giving 13.3 mg (18 %) of the title product. LCMS (an20p15): RT = 7.55 min, (M+1) = 495.

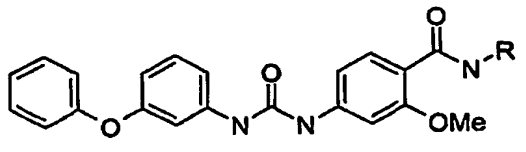
Example 117

2-Methoxy-*N*-(3-piperidin-1-yl-propyl)-4-[3-(3-trifluoromethyl-phenyl)-ureido]-benzamide

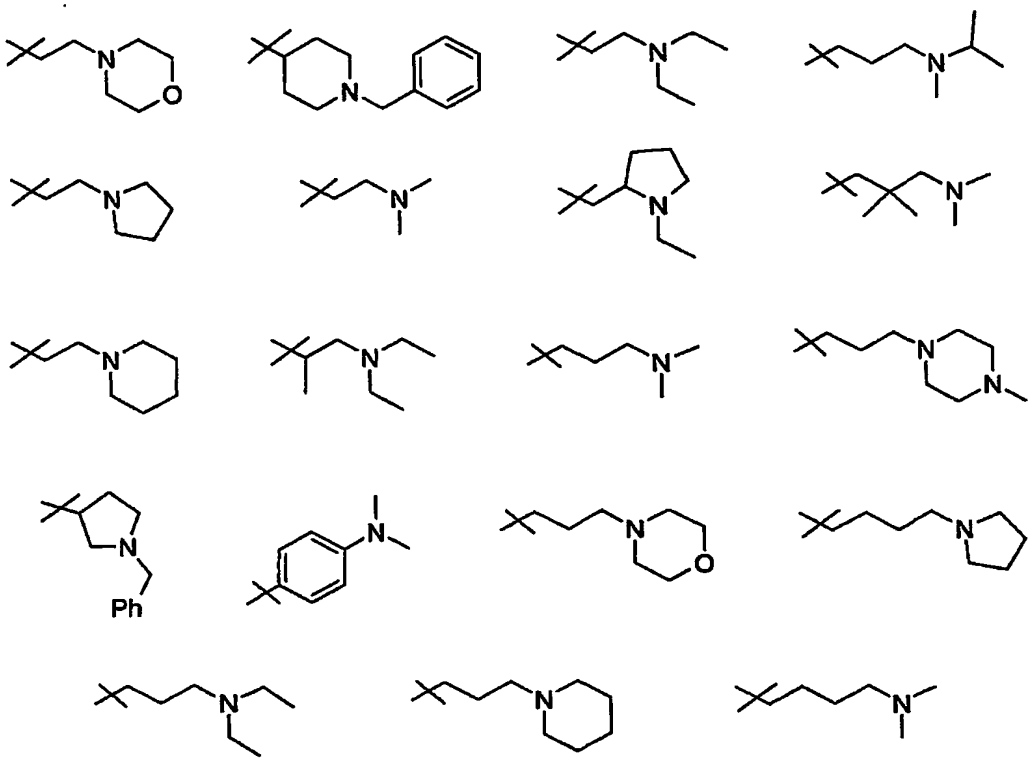
Ex 97 and 3-trifluorotosyl isocyanate were coupled giving 36.7 mg (38%) of the title product. LCMS (an20p15): RT = 6.19 min, (M+1) = 479.

According to the procedure described hereby the following compounds were prepared:
General procedure:

2-(3,5-Dimethoxy-4-formyl-phenoxy)ethyl polystyrene resin (200 mg, loading indicated by supplier 0.78 mmol/g, 0.16 mmol) was placed in a 12 mL fritted Teflon reactor fixed on an orbital shaker. A solution of amine (0.48 mmol, 3 eq) in NMP (1 mL), a solution of $NaCNBH_3$ (30 mg, 3 eq) in NMP (1 mL), AcOH (100 μL), and water (10 μL) was added to the resin. The mixture was shaken at room temperature over night. The resin was washed according to the general washing procedure described below. General washing procedure: NMP (2 mL), DCM (2 mL), MeOH (2 mL), DCM (2 mL), and NMP (2 mL). A solution of 2-methoxy-4-nitrobenzoic acid (99 mg, 3 eq) and 1-hydroxybenzotriazole (68 mg, 3 eq) in NMP/DCM (1 mL/1 mL) was added. Diisopropylcarbodiimide (80 μL, 3 eq) and diisopropylethylamine (30 μL, 1 eq) was added. The mixture was shaken at room temperature for 4 h, and hereafter the resin was washed according to the standard procedure. A solution of $SnCl_2 \bullet H_2O$ (180 mg, 5 eq) in NMP (2 mL) was added and diisopropylethylamine (30 μL, 1 eq) was added. The mixture was shaken over night at room temperature, and hereafter the resin was washed with NMP (2 mL), DCM (2 mL), MeOH (2 mL), 2×DCM (2 mL). The resin was treated with a solution of 3-phenoxyphenyl isocyanate (65 μL, 3 eq) in dry DCM (2 mL) and shaken at room temperature for 3 h. The resin was washed with NMP (2 mL), DCM (2 mL), MeOH (2 mL), 2× DCM (2 mL), and the treatment with 3-phenoxyphenyl isocyanate (65 μL, 3 eq) in dry DCM (2 mL) was repeated. Finally the resin was washed with NMP (2 mL), 5% diisopropylamine in NMP (2 mL), NMP (2 mL), DCM (2 mL), 5% AcOH in DCM (2 mL), DCM (2 mL), MeOH (2 mL), 3×DCM (2 mL). The resin was treated with TFA/DCM/TES (60:35:5, v/v, 2 mL) for 2 h at room temperature and hereafter washed with DCM (1 mL) to cleave the product from the resin. The samples were evaporated, redissolved in water/acetonitrile (2:8, v/v, 1 mL) and purified by preparative LC-MS. The compounds were eluted over 20 min with 20-95% acetonitrile in water (both solvents contained 0.01% TFA or 0.01% formic acid).



R =



Example 118

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

From the reaction was 91 mg of the crude product isolated giving after purification 13 mg (13%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.98 (s, 1H, NH^+), 8.49 (s, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 7.72 (d, 1 H, J = 7.7 Hz), 7.26-6.59 (m, 11 H), 3.91 (d, 2H, J = 12 Hz), 3.72 (s, 3H, OCH_3), 3.68 (s, 4H), 3.54 (d, 2H, J = 12 Hz), 3.23 (s, 2H), 2.88 (br t, 2H). LCMS(an10p15): RT = 8.39 min, (M+1) = 491.

Example 119

***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 161 mg of the crude product isolated giving after purification 37 mg (34%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H, NH^+), 8.41 (s, 1H), 8.20 (s, 1H), 7.83 (d, 1H, J = 6.8 Hz), 7.66 (d, 1 H, J = 7.7 Hz), 7.32-6.52 (m, 16 H), 3.97 (s, 3H), 3.67 (s, 3H, OCH_3), 3.35 (s, 2H), 2.64 (s, 2H), 2.01 (s, 2H), 1.81 (br s, 2H).
LCMS(an10p15): RT = 9.05 min, (M+1) = 551.

Example 120

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 97 mg of the crude product isolated giving after purification 6.6 mg (9%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.43 (s, 1H), 9.20 (s, 1H), 8.45 (m, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.39-6.39 (m, 9H), 3.84 (s, 3H, OCH_3), 3.78 (br s, 2H), 3.21 (m, 2H), 3.14 (m, 4H), 1.32 (t, J = 7.4 Hz, 6H). LCMS(an10p15): RT = 5.79 min, (M+1) = 477, RT = 7.19 min, (M+1) = 186, 20% (aniline from isocyanate)

Example 121

***N*-[3-(Isopropyl-methyl-amino)-propyl]-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

To a solution of 2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzoic acid (80 mg, 0.2 mmol), prepared using the same procedure as in example 45, in dichloromethane (20 mL) were HOBT (38mg, 0.27 mmol), EDAC (61 mg, 0.32 mmol), N^1-isopropyl-N^1-methyl-propyldiamine hydrochloride (52 mg, 0.25 mmol) and diisopropylethylamine (66 mg, 88 μL, 0.5 mmol) added and the stirring continued at room temperature over night. EtOAc was added to the reaction mixture and the organic phase was washed with NaHCO3 (sat). The aqueous phase was extracted with EtOAc and the combined organic phases was dried ($MgSO_4$) and concentrated giving the crude product. The crude product was chromatographed (silica, CH_2Cl_2/methanol, 85:15) followed by a SCX-colon and preparative LCMS giving 2.2 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.85 (s, 3H), 8.19 (t, 1H), 9.34 (s, 1H), 9.59 (s, 1H). LCMS (an20p15): (M+1) = 491.

Example 122

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide

From the reaction was 111 mg of the crude product isolated giving after purification 18 mg (20%)of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.71 (s, 1H), 8.74 (s, 1H), 8.49 (s, 1H), 8.29 (s, 1H), 7.65 (s, 1 H), 7.34-6.95 (m, 11 H), 3.65 (s, 3H), 3.62 (s, 4H), 3.18 (s, 2H), 2.75 (s, 2H), 1.92 (s, 4H). LCMS(an10p15): RT = 8.51 min , (M+1) = 475.

Example 123

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 113 mg of the crude product isolated giving after purification 21 mg (23%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.68 (s, 1H, NH^+), 8.70 (s, 1H), 8.42 (br s, 1H), 8.31 (s, 1H), 7.67 (d, 1 H, J = 7.5 Hz), 7.31-6.52 (m, 11 H), 3.69 (s, 3H, OCH_3), 3.59 (s, 2H), 3.31 (s, 2H), 2.76 (s, 6H). LC-MS(an20p15): RT = 8.30 min, (M+1) = 449.

Example 124

***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 124 mg of the crude product isolated giving after purification 10 mg (13%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.43 (s, 1H), 9.20 (s, 1H), 8.60 (t, 1H), 7.77 (d, J = 8.7 Hz, 1 H), 7.47 (s, 1H), 7.35-6.85 (m, 9 H), 6.59 (d, 1H), 3.83 (s, 3H, OCH_3), 3.59 (m, 4H), 3.21 (m, 1H), 2.81 (m, 2H), 2.13 (m, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.26 (t, , J = 7.2 Hz, 3H). LCMS(an10p15): RT = 5.90 min, (M+1) = 489.

Example 125

***N*-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

To a solution of 4-amino-*N*-(3-dimethylamino-2,2-dimethyl-propyl)-2-methoxy-benzamide (25 mg, 0.09 mmol), prepared according to the procedure for example 97, in dichloromethane (3 mL) was 3-phenoxyphenyl isocyanate (37 mg, 32 μL, 0.18 mmol) added and the reaction was stirred under inert atmosphere over night. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, CH_2Cl_2/methanol, 92:8) giving 37 mg of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 3.92 (s, 3H), 8.82 (t, 1H), 8.74 (s, 1H), 8.94 (s, 1H).

Example 126

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(2-piperidin-1-yl-ethyl)-benzamide

From the reaction was 90 mg of the crude product isolated giving after purification 18 mg (18 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.72 (s, 1H, NH^+), 9.09 (s, 1H), 8.80 (s, 1H), 8.33 (s, 1H), 7.67 (s, 1 H), 7.27-6.76 (m, 10 H), 6.52 (d, 1H, J = 7.2 Hz), 3.69 (s, 3H, OCH_3), 3.58 (s, 2H), 3.41 (s, 2H), 3.04 (s, 2H), 2.58 (s, 2H), 1.73 (s, 4H), 1.27 (s, 2H). LCMS(an10p15): RT = 8.76 min, (M+1) = 489.

Example 127

***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 118 mg of the crude product isolated giving after purification 17 mg (17%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.18 (s, 1H, NH^+), 9.04 (s, 1H), 8.72 (s, 1H), 8.27 (s, 1H), 7.69 (br d, 1 H), 7.32-6.50 (m, 11 H), 3.74 (s, 3H, OCH_3), 3.36 (s, 2H), 2.99 (br s, 4H), 2.90 (s, 3H), 1.88 (s, 1H), 1.16 (t, 6H, J = 7.1H Hz). LCMS(an10p15): RT = 8.65 min, (M+1) = 491.

Example 128

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 117 mg of the crude product isolated giving after purification 15 mg (16 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 10.86 (s, 1H, NH^+), 8.99 (s, 1H), 8.69 (s, 1H), 8.16 (s, 1H), 7.65 (d, 1 H, J = 7.5 Hz), 7.31-6.54 (m, 11 H), 3.73 (s, 3H, OCH_3), 3.35 (s, 2H), 2.91 (s, 2H), 2.67 (s, 6H), 1.88 (s, 2H). LCMS(an10p15): RT = 8.31 min, (M+1) = 463.

Example 129

2-Methoxy-*N*-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

From the reaction was 113 mg of the crude product isolated giving after purification 8.0 mg (7 %) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.92 (s, 1H), 9.84 (s, 1H,), 8.81 (t, 1H, J = 5.7 Hz, N*H*CO), 8.40 (d, 1H, J = 8.5 Hz), 8.08-7.61 (m, 11H, m), 7.27 (d, 1H, J = 7.5 Hz), 4.51 (s, 6H, OCH_3 + CH_3), 3.97 (br m, 6H), 3.63 (s, 2H), 3.43 (s, 4H), 3.31 (s, 2H). LCMS(an10p15): RT = 7.56 min, (M+1) = 518.

Example 130

***N*-(1-Benzyl-pyrrolidin-3-yl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 167 mg of the crude product isolated giving after purification 23 mg (22%) of the title product.^{1}H-NMR ($CDCl_3$): δ 11.61 (s, 1H, NH^+), 8.81 (s, 1H), 8.57 (s, 1H), 8.34 (s, 1H), 7.62 (br d, 1 H), 7.25-6.49 (m, 16 H), 4.55 (s, 1H), 4.05 (s, 3H, OCH_3), 3.06 (d, 4H), 3.36 (s, 1H), 3.13 (s, 1H), 2.79 (s, 1H), 2.37 (s, 1H). LCMS(an10p15): RT = 9.30 min, (M+1) = 537.

Example 131

***N*-(4-Dimethylamino-phenyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 122 mg of the crude product isolated giving after purification 25 mg (25%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.14 (s, 1H, NH^+), 8.53 (s, 1H), 8.21 (s, 1H), 7.73 (d, 1H, H = 9.0 Hz), 7.51 (d, 1 H, J = 8.7 Hz), 7.36-6.54 (m, 15 H), 3.79 (s, 3H, OCH_3), 3.03 (s, 6H). LCMS(an10p15): RT = 8.83 min, M+1 = 497.

Example 132

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide

The title product was prepared according to the procedure described in example **62**, giving after purification an isolated yield of 16.7 mg. ^{1}H-NMR (dmso-d_6): δ 3.89 (s, 3H), 8.04 (s, 1H), 9.09 (s, 1H), 9.12 (s, 1H). LCMS(an10p15): (M+1) = 497.

Example 133

2-Methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-*N*-(4-pyrrolidin-1-yl-butyl)-benzamide

From the reaction was 93 mg of the crude product isolated giving after purification 18 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.33 (s, 1H), 9.13 (s, 1H), 8.65 (s, 1H), 7.94 (t, J = 5.9 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1 H), 7.57 (s, 1H), 7.34-6.61 (m, 9H), 3.86 (s, 3H, OCH_3), 3.36 (m, 2H), 3.13 (br s, 4H), 2.99 (m, 2H), 1.98 (br s, 4H), 1.73 (m, 2H), 1.56 (m, 2H). LCMS(an20p10): RT = 5.76 min, (M+1) = 503.

Example 134

***N*-(3-Diethylamino-propyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 94 mg of the crude product isolated giving after purification 18 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.65 (s, 1H), 9.39 (s, 1H), 8.21 (t, 1H), 7.81 (d, 1 H), 7.50 (s, 1H), 7.22-6.85 (m, 9 H), 6.58 (d, 1H), 3.83 (s, 3H, OCH_3), 3.45 (br q, 2H), 3.05-2.91 (br m, 6H), 1.95 (br t, 2H), 1.23 (t, 6H, J = 7.2 Hz). LCMS(an10p15): RT = 8.62 min, (M+1) = 491.

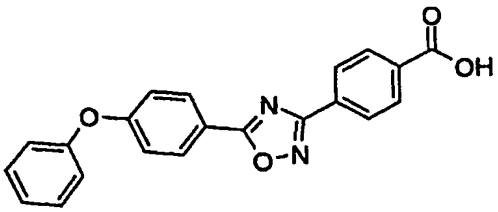
Example 135

***N*-(4-Dimethylamino-butyl)-2-methoxy-4-[3-(3-phenoxy-phenyl)-ureido]-benzamide**

From the reaction was 99 mg of the crude product isolated giving after purification 8.4 mg (20%) of the title product. ^{1}H-NMR ($CDCl_3$): δ 9.13 (s, 1H), 8.88 (s, 1H), 7.98 (t, J = 5.7 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1 H), 7.28 (s, 1H), 7.32-6.60 (m, 10 H), 3.83 (s, 3H, OCH_3), 3.35 (m, 2H), 2.93 (m, 2H), 2.66 (s, 6H), 2.02 (m, 2H), 1.56 (m, 2H). LCMS(an20p10): RT = 5.57 min, (M+1) = 477.

Example 136

4-[5-(4-Phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid

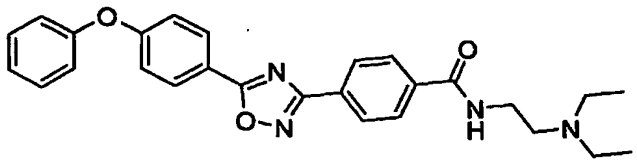


To a refluxing solution of 4-cyanobenzoic acid (3.6 g, 25 mmol) in dry THF (100 mL) was carbonyldiimidazole (3 x 2 g, 37.5 mmol) added in three portions with 20 min in between. The reaction was allowed to reflux for another hour before it was cooled to room temperature whereupon methanol (25 mL) was added. The reaction mixture was refluxed over night. The solvent was removed *in vacuo*. To the remaining solid was washed with water to give the Methyl-4-cyanobenzoate (3.8 g, 94%). Natrium (0.55 g, 24 mmol) was dissolved in methanol (5 mL) and after awhile was a solution of hydroxylamine hydrochloride (1.53 g, 22 mmol) in methanol (10 mL) added. This mixture was cooled and the formed NaCl was filtered off thereafter was methyl-4-cyanobenzoate (2.4 g, 15 mmol) dissolved in methanol (10 mL) added and the reaction mixture was stirred for three days. The solvent was removed *in vacuo* and the remains was stirred with water, filtered, and dried giving 1.13 g (58%) of the 4-(N-hydroxycarbamimidoyl)-benzoic acid methyl ester.To a cold solution of 4-phenoxybenzoic acid (0.34 g, 1.6 mmol) were oxalyl chloride (0.17 mL, 1.9 mmol) and a one drop of N,N-dimethylformamide added. The reaction mixture was stirred for 2 h and was allowed to reach room temperature during this time. This solution was used in next step. To an solution of 4-(N-hydroxycarbamimidoyl)-benzoic acid methyl ester (0.19 g, 1.0 mmol) (dichloromethane (5 mL) was diisopropylethylamine (0.5 mL, 2.8 mmol) added and the mixture was allowed to reach 0°C before the above prepared acid chloride-solution (6 mL, 0.96 mmol) was added drop wise. The reaction was stirred at room temperature for five days and thereafter poured into a mixture of EtOAc and water. The organic layer was separated, washed with brine followed by 0.05 N NaOH, dried over Na_2SO_4 and concentrated. The crude product was chromatographed (silica, EtOAc/petroleum ether, 1:1, Rf = 0.34) giving 0.32 g of the acylated product (80 %). This product was slurred in THF (10 mL) and 1.0 M tetrabutylammonium fluoride (0.10 mL, 0.1 mmol) was added whereupon the reaction became yellow. The reaction mixture was stirred for two days before it was quenched with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed (silica, EtOAc/petroleum ether, 1:1) giving 0.24 g of 4-[5-(4-Phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid methyl ester (84 %). This ester was hydrolysed by dissolving it in THF/methanol/water (10 mL, 6:3:1) and adding lithiumhydroxide (0.45 g, 19 mmol). The reaction mixture was stirred in room temperature over night. The solvents were removed in vacuo. Water (100 ml) was added to the

remains and the mixture was acidified (4N HCl) whereupon a precipitate was formed which were filtered and dried giving 0.16 g (74%). ^{1}H NMR (300 MHz, CD_3Cl): δ 7.1-7.2 (m, 4H), 7.29 (dt, 1H), 7.50 (2H), 8.13-8.17 (m, 2H), 8.19-8.24 (m, 4H).

Example 137

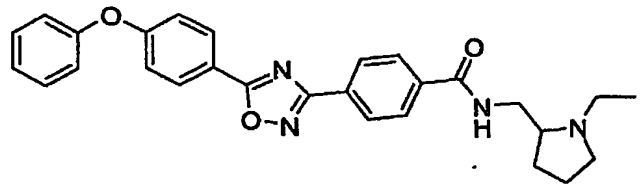
***N*-(2-Diethylamino-ethyl)-4-[5-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide**



Example 136 (40 mg, 0.11 mmol), PS-cabodiimidazole (0.15 g, 1.35 mmol/g), hydroxyl benztriazole (23 mg, 0.17 mmol), and *N,N*-diethylethylenediamine (14 □L, 0.10 mmol) were placed in a flask under nitrogen atmosphere with dichloromethane (2 mL) and the reaction was stirred for three days. PS-Trisamine (0.14 g, 3.58 mmol/g) and more dichloromethane (4 mL) were added and left stirring for 2h before the resins were filtered off. The solvent was removed *in vacuo*. The crude product was chromatographed (silica, dichloromethane/methanol/ammoniak, 95:5+0.5%) giving 20 mg (40%) of the title product. ^{1}H NMR (300 MHz, CD_3Cl): δ 1.07 (t, 6H), 2.60 (q, 4H), 7.13 (d, 4H).
LCMS (an20p10); Rt = 6.35 min, (M+1) = 457

Example 138

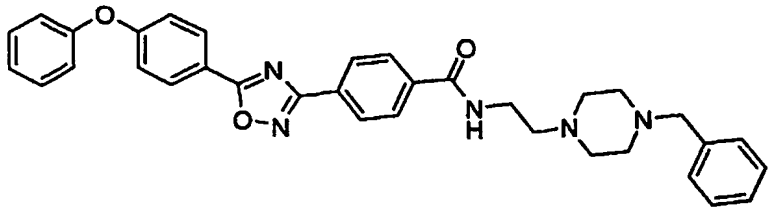
***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[5-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide**



The title product was synthesised using the same method as described in example 137 from example 136 (40 mg, 0.11 mmol) and 2-(4-benzylpiperazino)ethane-1-amine (27 μL, 0.10 mmol) giving 44 mg (70 %) of the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 2.03 (t, 6H), 2.93 (d, 2H), 3.56 (q, 4H), 7.93 (d, 2H), 7.45 (t, 2H). LCMS (an20p10); Rt = 7.40 min, M = 559

Example 139

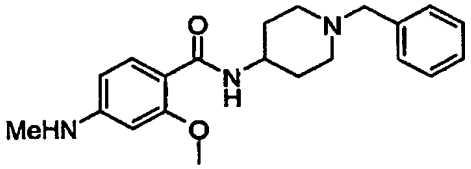
***N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[5-(4-phenoxy-phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide**



The title product was synthesised using the same method as described in example 137 from example 136 (40 mg, 0.11 mmol) and 2-(aminomethyl)-1-ethylpyrrolidine (15 μL, 0.13 mmol) giving 43 mg (81 %) of the product. ^{1}H NMR (300 MHz, CD_3Cl): δ 7.13 (d, 4H), 7.44 (t, 2H), 8.67 (s, 1H). LCMS (an20p10); Rt = 6.27 min, (M+1) = 469.

Example 140

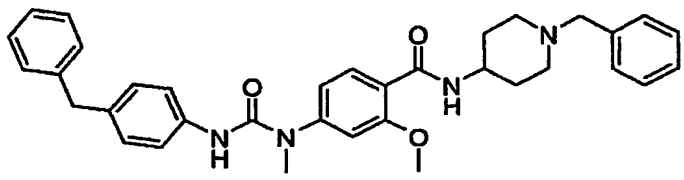
***N*-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-methylamino-benzamide**



4-Amino-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide (synthesised according to the same procedure as example 97) was dissolved in methanol and sodium methoxide (5.7 equiv.) and paraformaldehyde (1.5 equiv.) were added. The reaction was stirred over night under inert atmosphere at 40 °C. The mixture was cooled to room temperature whereupon sodium borohydride (2.4 equiv.) was added slowly and the reaction was continuously stirred over night at 50 °C. The solvent was removed *in vacuo*. The residue was dissolved in NaHCO3-solution (150 mL), extracted with *tert*-butylmethylether (3 x 100 mL). The combined organic phases was dried (Na2SO4) and concentrated. The crude product was chromatographed (silica, dichloromethane/methanol/ ammoniak, 100:10:1) giving the title product (78%). ^{1}H NMR (300 MHz, CD_3Cl): δ 2.89 (d, 3H, -NHMe).

Example 141

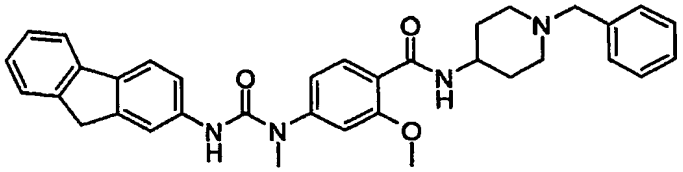
4-[3-(4-Benzyl-phenyl)-1-methyl-ureido]-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide



To a solution Ex 140 (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 4-benzylphenyl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 28 mg (87%) of the title product. LCMS (an20p15): RT = 6.75 min, (M+1) = 563.

Example 142

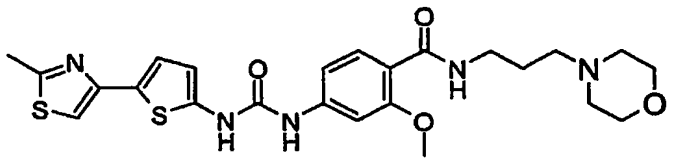
N-(1-Benzyl-piperidin-4-yl)-4-[3-(9H-fluoren-2-yl)-1-methyl-ureido]-2-methoxy-benzamide



To a solution Ex 140 (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 9H-fluoren-2-yl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 27 mg (85%) of the title product. LCMS (an20p15): RT = 6.62 min, (M+1) = 561.

Example 143

2-Methoxy-4-{3-[5-(2-methyl-thiazol-4-yl)-thiophen-2-yl]-ureido}-N-(3-morpholin-4-yl-propyl)-benzamide

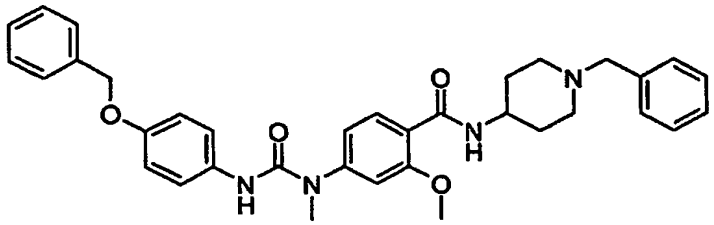


To a solution of 5-(2-methyl-1,3-thiazol-4-yl)thiophen-2-caboxylic acid (102 mg, 0.45 mmol) in toluene (5 mL) were dihenylphosphorylazid (79 μL, 0.37 mmol) and triethylamine (42 □L) added and therafter was the reaction mixture heated to reflux. After 3h was Ex. 61 (67 mg, 0.23 mmol) dissolved in hot toluene (2 mL) added. The reaction was allowed cooled a bit before dichloromethane (2 mL) was added and thereafter was the reaction left over night. The solvent was removed in vacuo. The crude product was purified with acidic ion exchange chromatography (SCX-colon) followed by one more chromatography (silica,

dichloromethane/methanol/ammoniak, 9:1+1%) giving 71 mg (61%) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 2.53 (s, 3H), 3.82 (s, 3H), 6.98 (dd, 1H), 8.07 (t, 1H), 9.08 (s, 1H), 9.83 (s, 1H).

Example 144

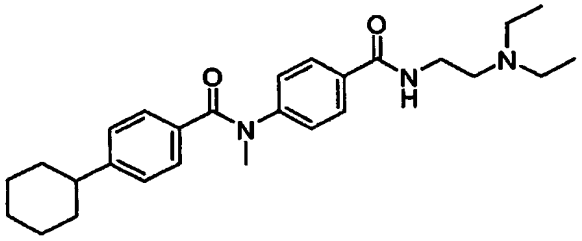
4-[3-(4-Benzyloxy-phenyl)-1-methyl-ureido]-*N*-(1-benzyl-piperidin-4-yl)-2-methoxy-benzamide



To a solution Ex 140 (20 mg, 0.057 mmol) in dichloromethane (0.5 mL) was 4-benzyloxy-phenyl isocyanate (24 mg, 0.11 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-trisamine (3.56 mmol/g, 100 mg) was added. After two days was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 28 mg (85%) of the title product. LCMS (an20p15): RT = 5.73 min, (M+1) = 579.

Example 145

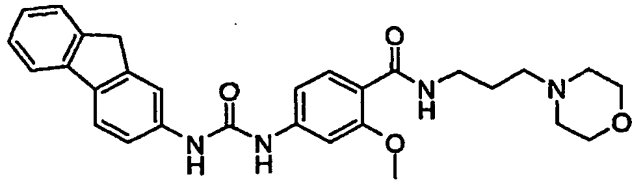
4-(4-cyclohexyl-*N*-methyl-benzamido)-N-(2-diethylaminoethyl)-benzamide



The title product was synthesised according to the same procedure described in example 30 and 2 with some following steps. The crude product was purified with acidic ion exchange chromatography (SCX-colon) giving 32 mg (18%) of the product. LCMS (an20p15): RT = 5.42 min, (M+1) = 436.2 m/z.

Example 146

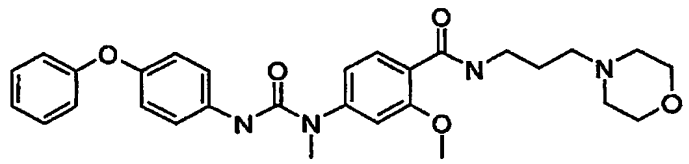
4-[3-(9H-Fluoren-2-yl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide)



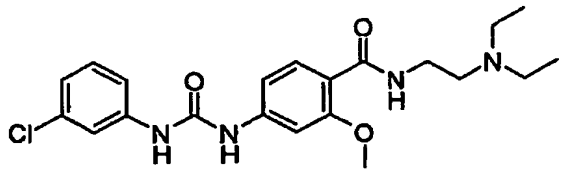
To a solution Ex 61 (20 mg, 0.068 mmol) in dichloromethane (0.5 mL) was 9H-fluoren-2-yl isocyanate (28 mg, 0.14 mml) added and the flask was flushed with nitrogen. The reaction mixture was stirred for four days when PS-tosyl chloride (1.0 equiv.) was added. After 12h was the resin filtered off and rinsed with dichloromethane. The reaction mixture was concentrated *in vacuo*. The crude product was purified with chromatography (dichloromethane/methanol, 92:8) giving 8.5 mg (25%) of the title product. ^{1}H NMR (300 MHz, dmso-d_6): δ 3.40 (s, 3H), 8.05 (t, 1H), 8.87 (s, 1H), 9.02 (s, 1H). LCMS (an20p15): (M+1) = 501 m/z.

Example 147

2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide



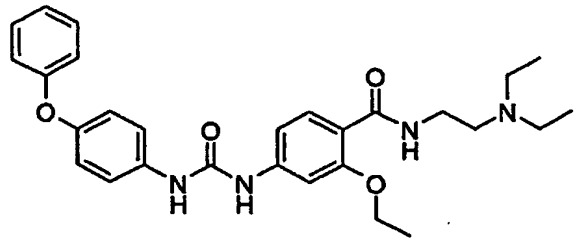
4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide



To a solution of 4-amino-N-(2-diethylamino-ethyl)-2-methoxy-benzamide (30 mg, 0.11 mmol) in dry dichloromethane (1.5 mL) was 3-chlorophenyl isocyanate (28 μL, 0.22 mmol) added and the reaction was stirred three days under inert atmosphere. PS-Trisamine (100 mg, 3.58 mmol/g) was added and after gentle stirring for 2 h, and addition of methanol (2 mL), was the resin removed by filtration. The resin was washed with dichloromethane (2 mL). The solvents were removed *in vacuo* and the crude product was purified through chromatography (silica, CH_2Cl_2/methanol/ammoniak, 101:10: 1) giving the desired product. ^{1}H-NMR (dmso-d_6): δ 0.99 (t, 4H), 2.20 (s, 2H), 3.90 (s, 3H), 8.98 (s, 1H), 9.07 (s, 1H). Mass analysis; found (M+1) = 419.

Example 148

***N*-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



A solution of methyl-4-acetamido-2-ethoxybenzoate (1g, 4.2 mmol) and lithium hydroxide (0.5g, 21 mmol) in a THF/water mixture (50ml/25ml) was heated to 70°C for 18h. After cooling, solvent was removed *in vacuo* to give a white semi-solid (0.788g, 4.2 mmol, 100%). ^{1}H NMR (300 MHz, D_2O): δ 1.2 (t, 3H), 3.95 (q, 2H), 6.25 (d, 1H), 6.35 (s, 1H), 7.2 (d, 1H).

To a cooled (0°C) solution of 4-amino-2-ethoxybenzoic acid, lithium salt (0.78g, 4.17 mmol) in a dioxane/water mixture (50ml/25ml) was added BOC_2O (0.92g, 4.17 mmol). After stirring for 10 minutes at 0°C, the reaction mixture was stirred at RT for 4h. The mixture was then cooled to 0°C and further BOC_2O (1.84g, 8.34 mmol) was added. After stirring for an additional 10 minutes at 0°C, the reaction mixture was stirred at RT for 2 days. Dioxane was removed *in vacuo*. The aqueous phase was diluted with water and washed with dichloromethane (3x). The aqueous phase was then saturated with NaCl, acidified with a 1N aq. HCl solution and quickly extracted with dichloromethane (3x). The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid as 4-Amino-2-ethoxy-benzoic acid (0.84 g, 2.96 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H), 1.55 (t, 3H), 4.35 (q, 2H), 6.69 (d, 1H), 6.75 (bs, 1H), 7.76 (s, 1H), 8.06 (d, 1H), 10.8 (bs, 1H)

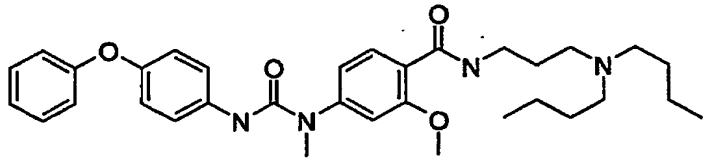
To a solution of 4-Amino-2-ethoxy-benzoic acid (0.1g, 0.35 mmol) in dichloromethane (20 ml) were added EDAC (0102 g, 0.53 mmol) and HOBt (0.062 g, 0.46 mmol). After stirring for 5 minutes, *N,N*-diethyl-ethylene diamine (60 µl, 0.43 mmol) was added and the reaction mixture was stirred at RT overnight. The mixture was washed with sat. aq. $NaHCO_3$ (3x), brine (2x), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil (0.135 g, 0.35 mmol, 100%). The oil was stirred overnight at RT in a TFA/dichloromethane mixture (3 ml/3 ml). Solvent was removed *in vacuo*. The residue was diluted with water and washed with dichloromethane (3x). The aqueous phase was saturated with NaCl and solid K_2CO_3 was added up to pH = 12. The aqueous phase was extracted with dichloromethane (3x), the organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a pale-brown oil as 4-Amino-

N-(2-diethylamino-ethyl)-2-ethoxy-benzamide (0.086 g, 0.31 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.04 (bt, 6H), 1.5 (t, 3H), 2.62 (bm,6H), 3.5 (bm, 2H), 3.92 (bs, 2H), 4.12 (q, 2H), 6.18 (s,1H), 6.32 (d, 1H), 8.03 (d, 1H), 8.2 (bs, 1H)

A solution of 4-Amino-*N*-(2-diethylamino-ethyl)-2-ethoxy-benzamide (0.08g, 0.286 mmol) and 4-phenoxyphenyl isocyanate (77.6 µl, 0.429 mmol) in dichloromethane (5 ml) was stirred at RT overnight under an argon atmosphere. PS-trisamine (0.286 mmol) was added and the reaction mixture was stirred for a further 18h00. Methanol (1 ml) was added to dissolve the precipitate. The resin was filtered off and the filtrate was concentrated to give a semi-solid which was triturated with methanol. The solid was filtered, washed with methanol and dried *in vacuo* to give a white powder (0.08 g, 0.163 mmol, 57%). ^{1}H NMR (300 MHz, DMSO): δ 0.97 (t, 6H), 1.45 (t, 3H), 2.53 (m, 6H), 3.35 (q, 2H), 4.18 (q, 2H), 6.95-7.5 (m, 11H), 7.85 (d, 1H), 8.2 (bm, 1H), 8.76 (s, 1H), 8.94 (s, 1H)

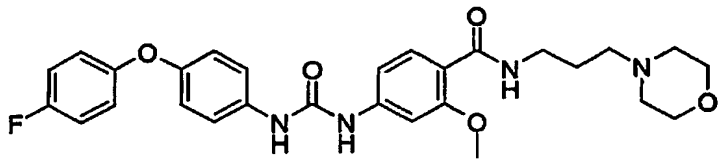
Example 149

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide**



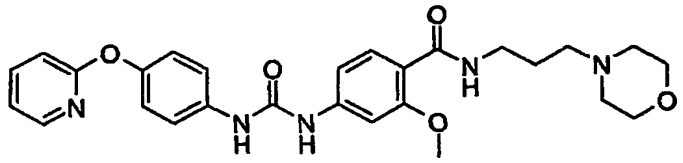
Example 150

4-{3-[4-(4-Fluoro-phenoxy)-phenyl]-ureido}-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide



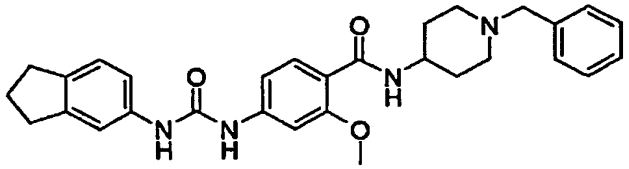
Example 151

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-{3-[4-(pyridin-2-yloxy)-phenyl]-ureido}-benzamide



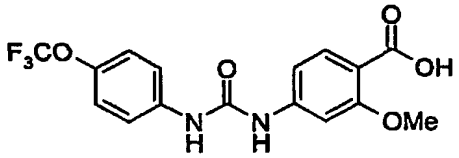
Example 152

***N*-(1-Benzyl-piperidin-4-yl)-4-(3-indan-5-yl-ureido)-2-methoxy-benzamide**



Example 153

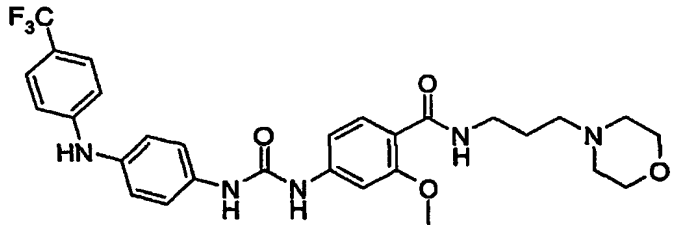
2-Methoxy-4-[3-(4-trifluoromethoxy-phenyl)-ureido]-benzoic acid



Using the same procedure as described in example 45 was the title product synthesised from 4-amino-2-methoxy-benzoic acid and 4-trifluoromethoxyphenyl isocyanate giving the title product.

Example 154

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-{3-[4-(4-trifluoromethyl-phenylamino)-phenyl]-ureido}-benzamide



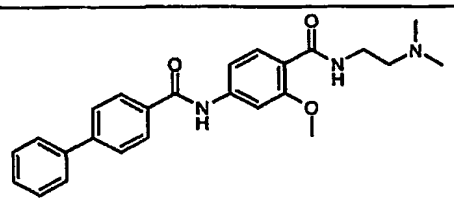
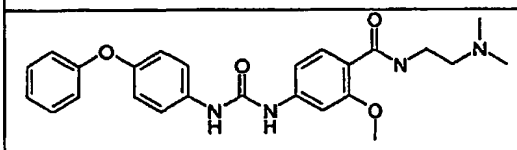
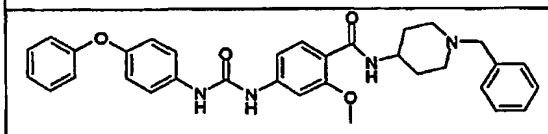
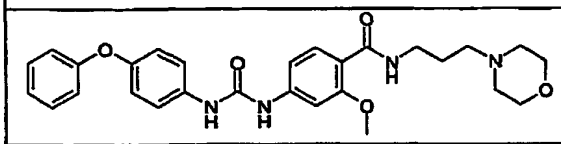
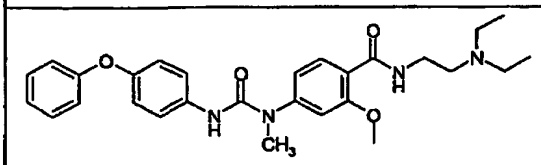
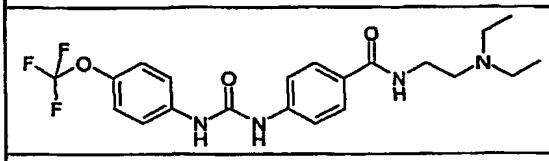
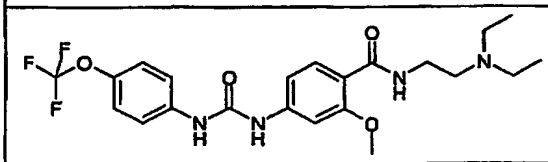
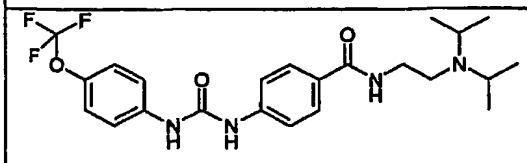
Following the same general procedure as described in example 99 was **Ex 61** (57 mg, 0.20 mmol) and 4-(4-Trifluoromethyl-phenylamino)-benzoic acid (0.10 g, 0.36 mmol) giving 52 mg (45%) of the title product. LCMS (an20p15): (M+1) = 572 m/z

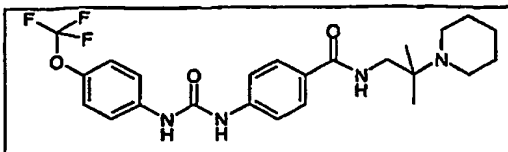
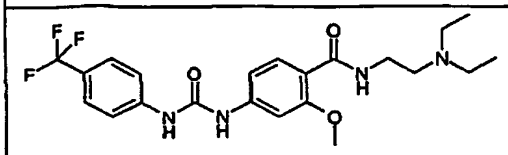
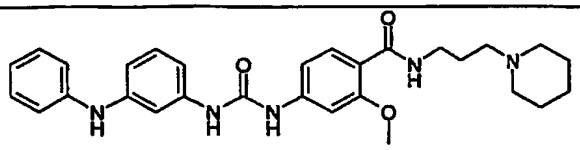
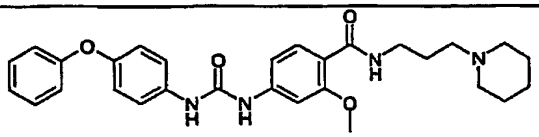
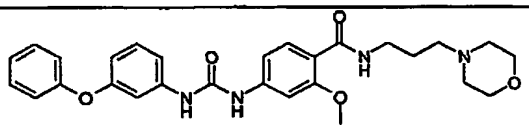
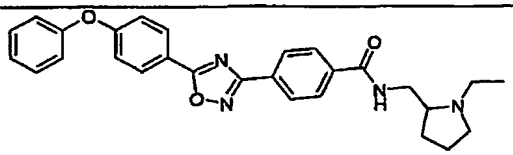
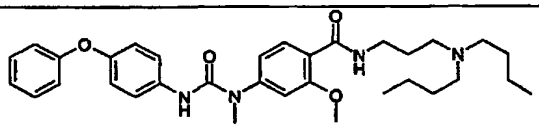
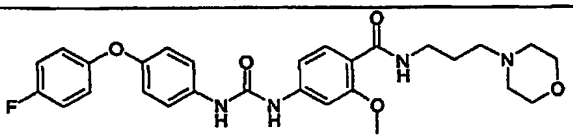
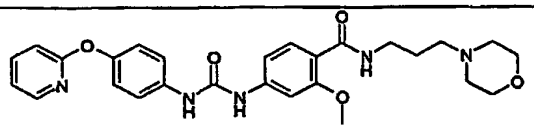
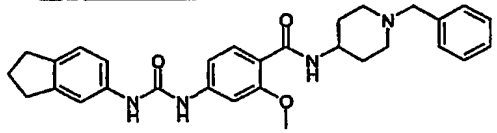
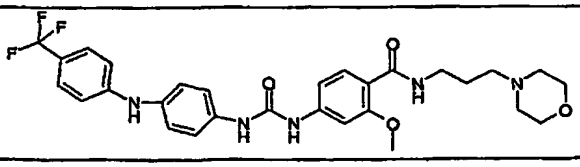
Example 155

***In vitro* tests of compounds according to the invention**

The following results were obtained

Receptor binding data

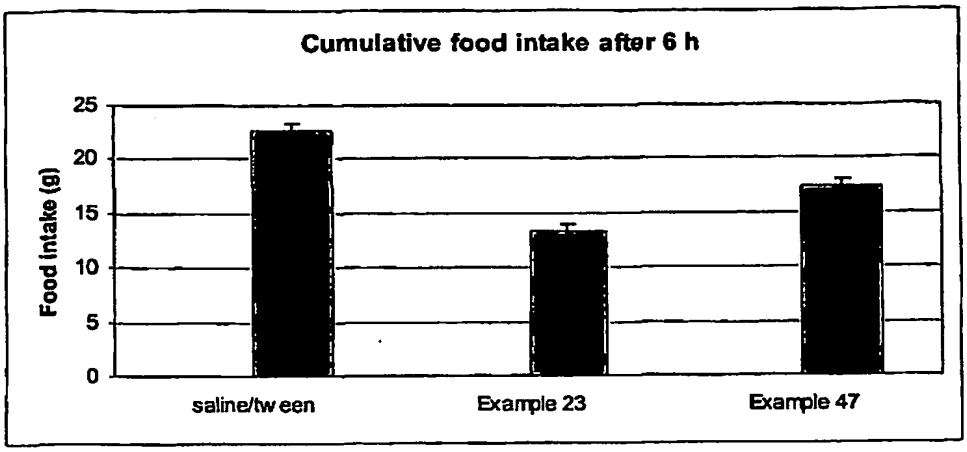
Compound	Example	Receptor binding IC_{50} µM	IP3 IC_{50} µM
	**Ex 2**	1.48	
	**Ex 8**	0.38	2.3
	**Ex 16**	0.22	1.8
	**Ex 23**	0.21	0.77
	**Ex 33**	0.048	0.29
	**Ex 47**	0.07	0.29
	**Ex 48**	0.096	0.19
	**Ex 67**	0.13 (SPA)	0.89

	**Ex 73**	0.70 (SPA)	
	**Ex 78**	0.027 (SPA)	0.22
	**Ex 100**	0.012	0.022
	**Ex 106**	0.044	0.24
	**Ex132**	0.074	0.11
	**Ex 138**	1.90	
	**Ex149**	0.069	0.67
	**Ex 150**	0.45	1.6
	**Ex 151**	4.45	
	**Ex 152**	0.30	
	**Ex 154**	1.41	

Example 156

***In vivo* tests of compounds according to the Invention**

The following results were obtained on reduction in food intake.



The following compounds are prepared as described in previous examples.

The following compounds are prepared as described in previous examples.

4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide
N-(2-Dimethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-(2-Diethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide
N-{3-[4-(3-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-ureido)-benzamide
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-1-methyl-ureido)-benzamide
4-[3-(4-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide
4-[3-(4-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide
2-Methoxy-4-[3-(4-methoxy-phenyl)-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

2-Methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-ureido)-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-1-methyl-ureido)-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

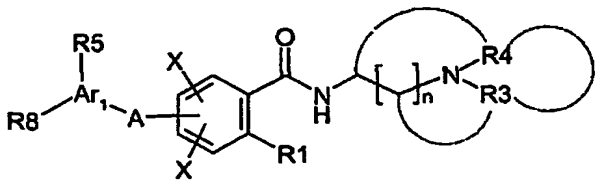
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(1-methyl-3-phenyl-ureido)-benzamide

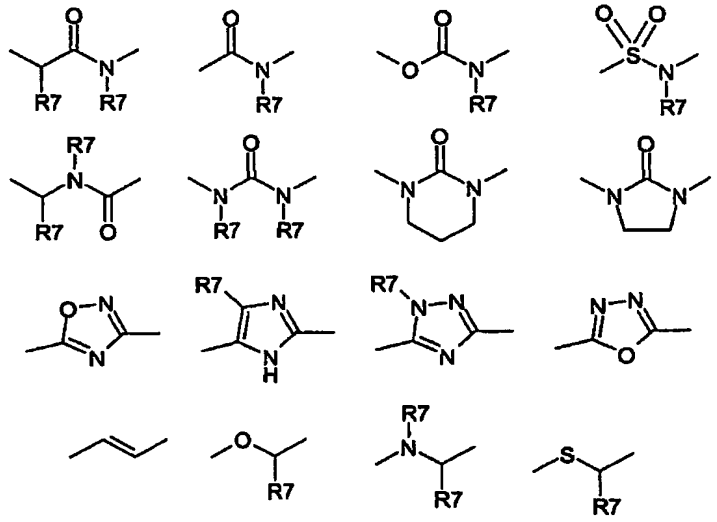
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(3-phenyl-ureido)-benzamide

CLAIMS

1. A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



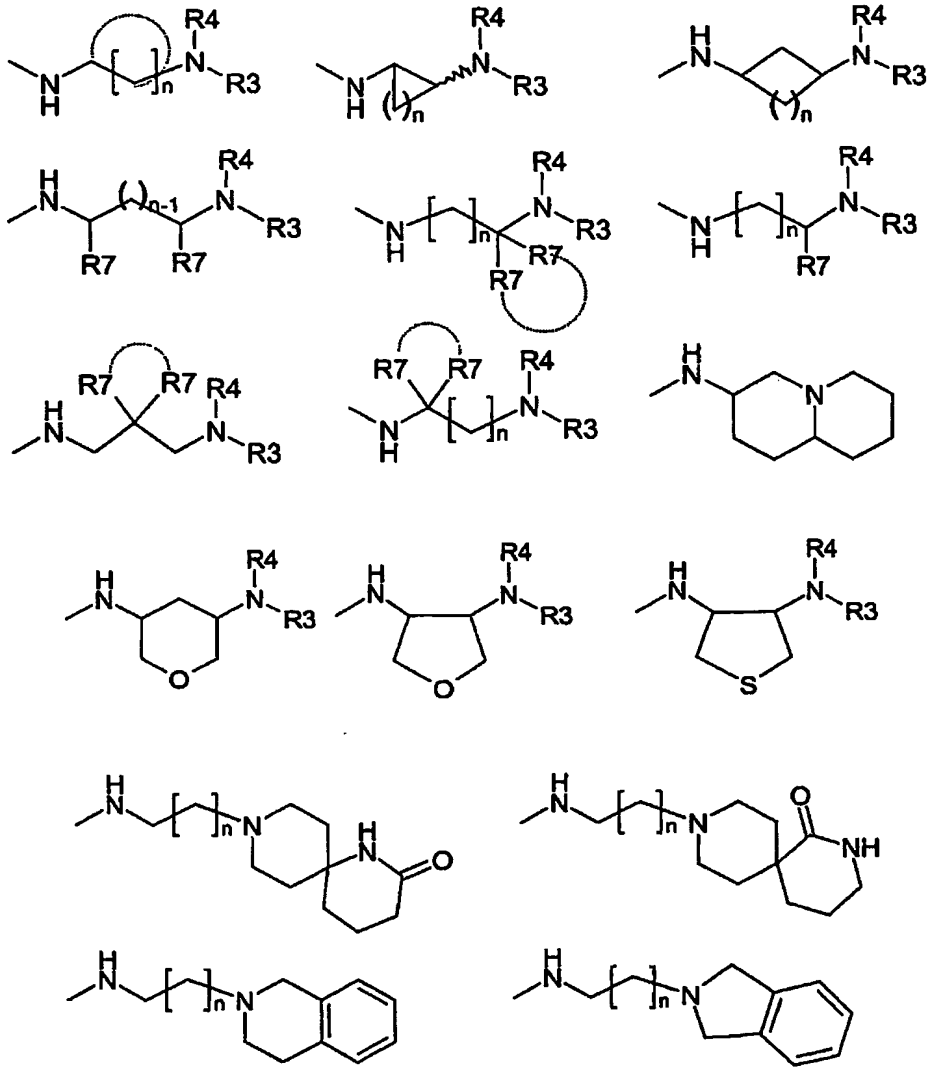
and, wherein the linker may be attached via either of the two free bonds to the Ar1 group;

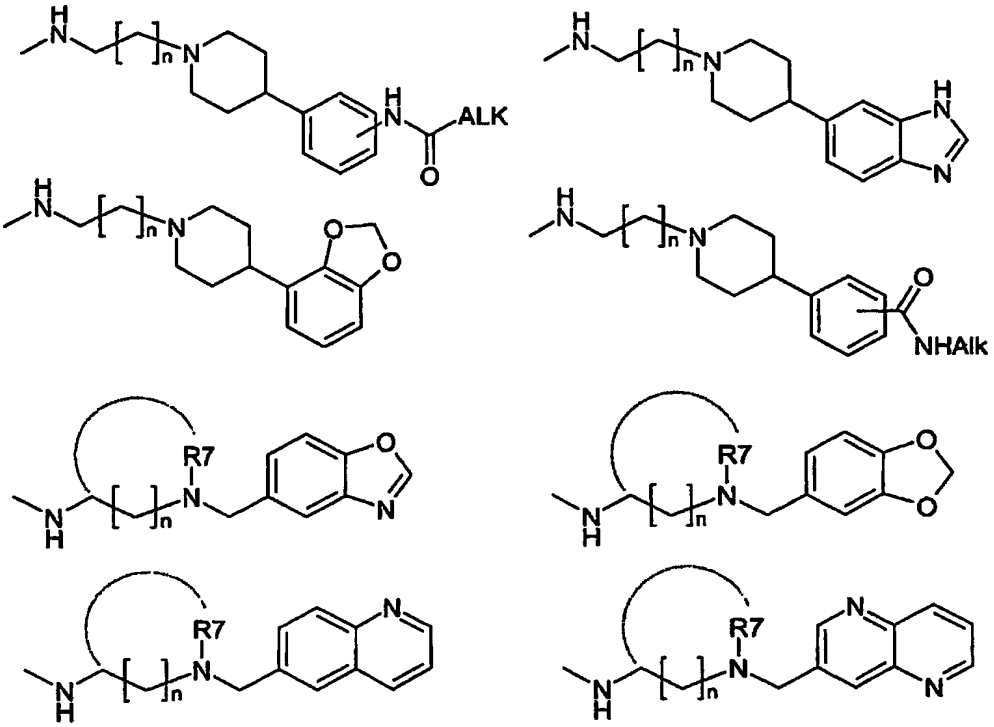
and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

Ar_1 is an aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 is hydrogen or a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon, and in the case of R1 being ethoxy or propoxy it may be annelated with the benzene ring;

R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbons; alkylcycloalkyl with 4-9 carbons atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, $-CONH_2$, -CONHAlk, $-CONAlk_2$, or fused moieties such as $-O-CH_2-O-$, -N=CH-NH-, -O-CH=N-, -N=CH-CH=CH- ; examples of more complex motifs are





Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 or R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 may the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3; -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

R8 is hydrogen, halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), arylamino groups (Ar-NR7-, ArNH-), arylalkylamino groups (ArAlkNH-, ArAlkNR7-, $ArCH_2NR7$-, $ArCH_2NH$-), alkoxy groups (AlkO-), alkylamino groups (AlkNH-) dialkylamino groups (Alk_2N-), -$CONH_2$, -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -CF_2-Ar, -$N(CF_3)_2$, -SCH_3, partially or fully

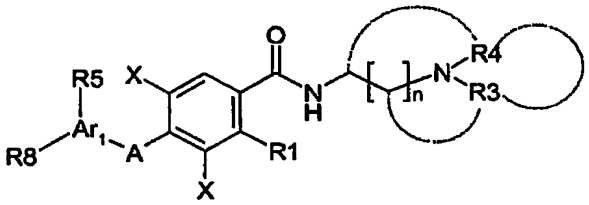
fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$;

more than one R5 group, same or different, may be present on Ar1; when more than one R5 or when one R5 and one R8 group are present they could be connected to each other, directly or with a suitable connecting molety, to form rings.

X being the same or different H, F, Cl, Br, I, $-SCH_3$, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as $-CH_2CF_3$, $-CF_2CF_3$, $-CF_3$, $-OCF_3$, $-SCF_3$; OCH_3 or lower alkyl or alkenyl group;

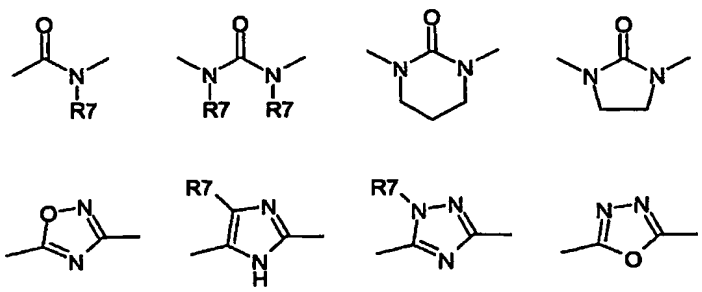
n is 1,2 or 3, and the alkyl chain connecting the amide nitrogen and the aliphatic nitrogen may optionally be substituted with one or more R7, alkyl or heteroalkyl groups, which optionally may form a ring;

2. A compound according to claim 1 with the following structure (Formula Ia)

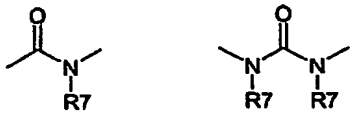


wherein Ar_1, A, B, R1, R3, R4, R5, R8, n and X are as defined in claim 1.

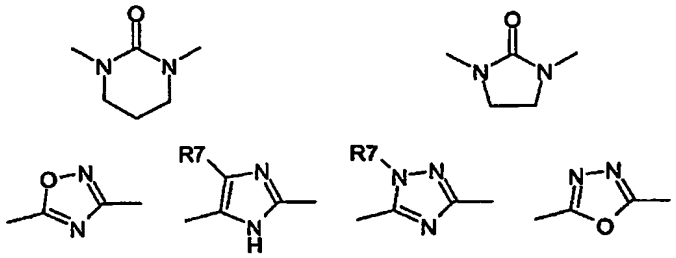
3. A compound according to claim 1 or 2, wherein -A- is selected from the group consisting of



4. A compound according to any of the preceding claims, wherein the –A- moiety is selected from the group consisting of



5. A compound according to any of claims 1-3, wherein the –A- moiety is selected from the group consisting of



6. A compound according any of the preceding claims, wherein R8 is hydrogen, halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3;

7. A compound according to any of claims 1-5, wherein R8 is aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups, alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), -arylamino groups (ArNH- or ArNR7-), arylalkylamino groups (ArAlkNH-, ArAlkNR7-, $ArCH_2NR7$-, $ArCH_2NH$-), CONHAr, -NHCO-Ar, -CF_2-Ar, or -CO-Ar.

8. A compound according to claim 6, wherein R8 is -SCH_3, partially or fully fluorinated alkyl, alkoxy or thioalkoxy groups such as -CH_2CF_3, -CF_2CF_3, -CF_3, -OCF_3, -SCF_3.

9. A compound according to any of the preceding claims, wherein Ar_1 is an aryl or heteroaryl group such as, e.g. phenyl, pyridine, thiophene.

10. A compound according to any of the preceding claims, wherein X is H, F, Cl, or lower alkyl.

11. A compound according to any of the preceding claims, wherein R5 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

12. A compound according to any of the preceding claims in amorphous or crystalline form.

13. A compound according to any of the preceding claims in racemic or enantiomeric form.

14. A compound according to any of the preceding claims in the form of a physiologically acceptable salt, complex, solvate or prodrug thereof.

15. A compound according to any of the preceding claims for use in medicine.

16. A compound according to any of the preceding claims, which is an agent for preventing or treating diseases caused by or involving a melanin-concentrating hormone.

17. A compound according to any of the preceding claims, which is modulating the activity of a MCH receptor.

18. A compound according to any of the preceding claims, which has antagonistic activity against a MCH receptor.

19. A compound according to any claim 1-17, which has agonistic, inverse agonistic or allosteric activity against a MCH receptor.

20. A compound according to any of the preceding claims, wherein the MCH receptor has at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequence CTLITAMDAN or CTIITSLDTC

21. A compound according to any of the preceding claims, wherein the MCH receptor comprises the amino acid sequence CTLITAMDAN or CTIITSLDTC.

22. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 or MCH2 receptor.

23. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 receptor.

24. A compound according to any of the preceding claims, wherein the MCH receptor is a mammalian such as human receptor.

25. A compound according to any of the preceding claims, which is an agent for preventing or treating feeding disorders.

26. A compound according to any of claims 1-18 or 20-25, which is an agent for reducing body mass.

27. A compound according to any of claims 1-18 or 20-26, which is an agent for preventing or treating Syndrome X (metabolic syndrome), or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension.

28. A compound according to any of claims 1-18 or 20-27, which is an agent for preventing or treating Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM).

29. A compound according to any of claims 1-18 or 20-28, which is an agent for preventing or treating bulimia, obesity and/or bulimina nervosa.

30. A compound according to any of claims 1-24, which is an antidepressant and/or anti-anxiety agent.

31. A cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to any of claims 1-18 or 20-29.

32. A method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-30.

33. A method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-29.

34. A method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-29.

35. A method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-18 or 20-29.

36. A method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-18 or 20-29.

37. A method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-18 or 20-29.

38. A method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-18 or 20-29.

39. A method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-19 or 30.

40. A pharmaceutical composition comprising a compound according to any of the claims 1-30 or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

41. A pharmaceutical composition according to claim 40, wherein the compound is present in the form of a physiologically acceptable salt such as a salt formed between the compound and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a

hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_6 salt, or a salt formed between the compound and an organic acid such as organic acids like e.g. H_2CO_3, acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

42. A pharmaceutical composition according to claim 40 or 41 for enteral and/or parenteral use.

43. A pharmaceutical composition according to claim 40 or 41 for oral, buccal, rectal, nasal, topical, vaginal or ocular use.

44. A pharmaceutical composition according to any of claims 40-43 in the form of a solid, semi-solid or fluid composition.

45. A pharmaceutical composition according to claim 44 in solid form, wherein the composition is in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, or particulate material.

46. A pharmaceutical composition according to claim 44 in semi-solid form, wherein the composition is in the form of a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

47. A pharmaceutical composition according to claim 44 in fluid form, wherein the composition is in the form of a solution, an emulsion, a suspension, a dispersion, a liposomal composition, a spray, a mixture, or a syrup.

48. A pharmaceutical composition according to any of claims 41-47 comprising a therapeutically effective amount of a compound according to claims.

49. A pharmaceutical composition according to claim 48, wherein the amount is from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

50. Use of a compound according to any of the claims 1-18 or 20-29 or a pharmaceutically acceptable salt thereof for the manufacture of a cosmetic composition for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto.

51. Use of a compound according to any of the claims 1-30 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for i) the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, ii) the treatment and/or prophylaxis of diseases caused by feeding disorders, iii) modifying the feeding behaviour of a mammal, iv) the reduction of body mass, v) the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, or vi) the treatment and/or prophylaxis of depression and/or anxiety.

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